

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
10 October 2002 (10.10.2002)

PCT

(10) International Publication Number
WO 02/079143 A1(51) International Patent Classification⁷: C07C 235/82, 255/60, C07D 231/56, 311/74, C07C 323/40, C07D 307/79, 213/40, 215/12, 319/20, 317/52, A61K 31/195, 31/335, 31/41, 31/435, A61P 15/00

(21) International Application Number: PCT/IB02/00807

(22) International Filing Date: 18 March 2002 (18.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

| | | |
|-----------|-----------------------------|----|
| 0107750.2 | 28 March 2001 (28.03.2001) | GB |
| 0113112.7 | 30 May 2001 (30.05.2001) | GB |
| 0120152.4 | 17 August 2001 (17.08.2001) | GB |

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/079143 A1

(54) Title: N-PHENPROPYLCYCLOPENTYL-SUBSTITUTED GLUTARAMIDE DERIVATIVES AS NEP INHIBITORS FOR FSAD

(57) Abstract: The invention relates to compounds of formula (I) for treating for example sexual dysfunction, wherein R¹ is optionally substituted C₁₋₆alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, hydrogen, C₁₋₆alkoxy, -NR₂R³ or -NR⁴SO₂R⁵; X is the linkage -(CH₂)_n- or -(CH₂)_q-O- (wherein Y is attached to the oxygen); wherein one or more hydrogen atoms in linkage X may be replaced independently by C₁₋₄alkoxy; hydroxy; hydroxy(C₁₋₃alkyl); C₃₋₇cycloalkyl; carbocyclyl; heterocyclyl; or by C₁₋₄alkyl optionally substituted by one or more fluoro or phenyl groups; n is 3, 4, 5, 6, or 7; and q is 2, 3, 4, 5 or 6; and Y is phenyl or pyridyl, each of which may be substituted; or two R⁸ groups on adjacent carbon atoms together with the interconnecting carbon atoms may form a fused optionally substituted 5- or 6-membered carbocyclic or heterocyclic ring.

N-Phenpropylcyclopentyl-Substituted Glutaramide Derivatives as NEP Inhibitors for FSAD

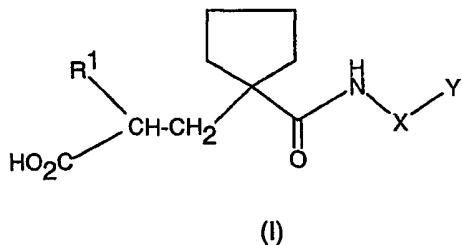
The invention relates to inhibitors of neutral endopeptidase enzyme (NEP), uses thereof, processes for the preparation thereof, intermediates used in the preparation thereof and compositions containing said inhibitors. These inhibitors have utility in a variety of therapeutic areas including the treatment of male and female sexual dysfunction, particularly female sexual dysfunction (FSD), especially wherein the FSD is female sexual arousal disorder (FSAD).

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NEP inhibitors are disclosed in WO 91/07386 and WO 91/10644.

The use of NEP inhibitors for treating FSD is disclosed in EP1 097 719-A1.

15 According to a first aspect, the invention provides a compound of formula (I), a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof;



wherein

20 R^1 is C_{1-6} alkyl which may be substituted by one or more substituents, which may be the same or different, selected from the list: halo, hydroxy, C_{1-6} alkoxy, hydroxy C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, carbocyclyl (preferably C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl or phenyl), carbocyclyoxy (preferably phenoxy), C_{1-4} alkoxycarbocyclyoxy (preferably C_{1-4} alkoxyphenoxy), heterocyclyl, heterocyclyoxy, $-NR^2R^3$, $-NR^4COR^5$, $-NR^4SO_2R^5$, $-CONR^2R^3$, $-S(O)_pR^6$, $-COR^7$ and $-CO_2(C_{1-4}$ alkyl); or R^1 is carbocyclyl (preferably C_{3-7} cycloalkyl or phenyl) or heterocyclyl, each of which may be substituted by one or more substituents from said list, which substituents may be the same or different, which list further includes C_{1-6} alkyl; or R^1 is hydrogen, C_{1-6} alkoxy, $-NR^2R^3$ or $-NR^4SO_2R^5$;

25

wherein

R² and R³, which may be the same or different, are carbocyclyl (preferably C₃-7cycloalkyl or phenyl) or heterocyclyl (each of which may be substituted by C₁-4alkyl, hydroxy or C₁-4alkoxy); or are hydrogen or

5 C₁-4alkyl; or R² and R³ together with the nitrogen to which they are attached form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C₁-4alkyl)piperazinyl group;

R⁴ is hydrogen or C₁-4alkyl;

10 R⁵ is C₁-4alkyl, CF₃, carbocyclyl (preferably phenyl), C₁-4alkylcarbocyclyl (preferably C₁-4alkylphenyl), C₁-4alkoxycarbocyclyl (preferably C₁-4alkoxyphenyl), heterocyclyl, C₁-4alkoxy or -NR²R³;

R⁶ is C₁-4alkyl, carbocyclyl (preferably phenyl), heterocyclyl or NR²R³; and

15 R⁷ is C₁-4alkyl, carbocyclyl (preferably C₃-7cycloalkyl or phenyl) or heterocyclyl;

p is 0, 1, 2 or 3;

X is the linkage -(CH₂)_n- or -(CH₂)_q-O- (wherein Y is attached to the oxygen); wherein one or more hydrogen atoms in linkage X may be replaced independently by C₁-4alkoxy; hydroxy; hydroxyC₁-3alkyl; C₃-7cycloalkyl; carbocyclyl; heterocyclyl; or by C₁-4alkyl optionally substituted by one or more fluoro or phenyl groups; n is 3, 4, 5, 6 or 7; and q is 2, 3, 4, 5 or 6; and

20 Y is phenyl or pyridyl, each of which may be substituted by one or more groups R⁸ which may be the same or different, wherein R⁸ is hydroxy; mercapto; halogen; cyano; acyl; amino; mono(C₁-4alkyl)amino; di(C₁-4alkyl)amino; carbocyclyl or heterocyclyl (either of which is optionally substituted by C₁-6alkyl, haloC₁-6alkyl, C₁-6alkoxy, haloC₁-6alkoxy, C₁-6alkylthio or halogen); C₁-6alkoxy; phenoxy; C₁-6alkylthio; phenylthio; or alkyl optionally substituted by C₁-6alkoxy, haloC₁-6alkoxy, C₁-6alkylthio, halogen or phenyl; or

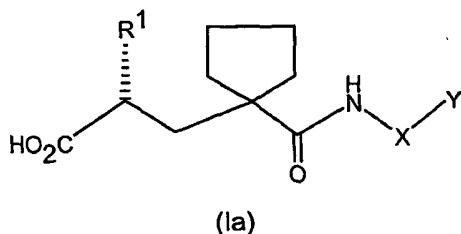
25 two R⁸ groups on adjacent carbon atoms together with the interconnecting carbon atoms may form a fused 5- or 6-membered carbocyclic or heterocyclic ring, optionally substituted by C₁-6alkyl, haloC₁-6alkyl, C₁-6alkoxy, haloC₁-6alkoxy, C₁-6alkylthio or halogen.

Preferably R¹ is hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₃alkyl, C₁₋₆alkoxyC₁₋₆alkoxyC₁₋₃alkyl or C₁₋₆alkyl substituted by phenyl.

5 More preferably R¹ is hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₃alkyl (preferably methoxyC₁₋₃alkyl) or C₁₋₆alkoxyC₁₋₆alkoxyC₁₋₃alkyl (preferably methoxyethoxymethyl).

More preferably still R¹ is C₁₋₄alkyl (preferably propyl) or C₁₋₆alkoxyC₁₋₃alkyl (preferably methoxyC₁₋₃alkyl, more preferably methoxyethyl).

A preferred group of compounds are of formula Ia:



15 Preferably n is 3 or 4, more preferably 3.

Preferably q is 2 or 3, more preferably 2.

Preferably X is -(CH₂)_n- wherein one or more hydrogen atoms in linkage X may be replaced by one or more of the groups defined for X in the first aspect.

Preferably R⁸ is C₁₋₆alkyl, C₁₋₆alkoxy, hydroxy, mercapto, halo, cyano, carbocyclyl or heterocyclyl; or two R⁸ groups on adjacent carbon atoms together with the interconnecting carbon atoms may form a fused 5- or 6-membered carbocyclic or heterocyclic ring, optionally substituted by C₁₋₆alkyl, haloC₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkoxy, C₁₋₆alkylthio or halogen.

When R⁸ is carbocyclyl, preferred groups are cyclopentyl, cyclopropyl, cyclohexyl or phenyl.

When R^8 is heterocycl, preferred groups are pyridyl, oxadiazolyl, pyrazolyl or triazolyl.

When Y is phenyl and two R^8 groups on adjacent carbon atoms together with the interconnecting carbon atoms form a fused 5- or 6-membered carbocyclic or

5 heterocyclic ring, preferred fused ring systems are naphthyl, quinolinyl, isoquinolinyl, indolyl, indazolyl, benzimidazolyl, benzisoxazolyl, dihydrobenzofuranyl, benzoxazolyl, indanyl, benzisothiazolyl and benzothiazolyl.

Preferred compounds of the invention are:

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(2R)-2-{{1-({[3-(4-methoxyphenyl)propyl]amino}carbonyl)cyclopentyl}methyl}pentanoic acid (Example 16),
3-{{1-({[3-(4-methoxyphenyl)propyl]amino}carbonyl)cyclopentyl}propanoic acid (Example 18),

15

3-{{1-({[3-(2,3-dihydro-1-benzofuran-5-yl)propyl]amino}carbonyl)cyclopentyl}propanoic acid (Example 21),
2-{{1-({[3-(4-chlorophenyl)propyl]amino}carbonyl)cyclopentyl}methyl}-4-methoxybutanoic acid (Example 15),
2-{{1-({[3-(4-fluorophenyl)propyl]amino}carbonyl)cyclopentyl}methyl}-4-methoxybutanoic

20

acid (Example 4),
4-methoxy-2-{{1-({[3-(4-methoxyphenyl)propyl]amino}carbonyl)cyclopentyl}-methyl}butanoic acid (Example 1),
2-{{1-({[3-(2,3-dihydro-1-benzofuran-5-yl)propyl]amino}carbonyl)cyclopentyl}-methyl}-4-methoxybutanoic acid (Example 11),

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(2S)-2-{{1-({[3-(4-chlorophenyl)propyl]amino}carbonyl)cyclopentyl}methyl}-4-methoxybutanoic acid (Example 22), and
(2S)-2-{{1-({[3-(2,3-dihydro-1-benzofuran-5-yl)propyl]amino}carbonyl)cyclopentyl}-methyl}-4-methoxybutanoic acid (Example 25).

30

A particularly preferred compound is (2S)-2-{{1-({[3-(4-chlorophenyl)propyl]amino}carbonyl)cyclopentyl}methyl}-4-methoxybutanoic acid (Example 22).

Unless otherwise indicated, any alkyl group may be straight or branched and is of 1 to 6 carbon atoms, preferably 1 to 4 and particularly 1 to 3 carbon atoms.

Unless otherwise indicated, any carbocyclyl group contains 3 to 8 ring-atoms, and may be saturated, unsaturated or aromatic. Preferred saturated carbocyclyl groups are cyclopropyl, cyclopentyl or cyclohexyl. Preferred unsaturated carbocyclyl groups contain up to 3 double bonds. A preferred aromatic carbocyclyl group is phenyl. The term 5 carbocyclic should be similarly construed. In addition, the term carbocyclyl includes any fused combination of carbocyclyl groups, for example naphthyl, phenanthryl, indanyl and indenyl.

Unless otherwise indicated, any heterocyclyl group contains 5 to 7 ring-atoms up to 4 of 10 which may be hetero-atoms such as nitrogen, oxygen and sulfur, and may be saturated, unsaturated or aromatic. Examples of heterocyclyl groups are furyl, thienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, dioxolanyl, oxazolyl, thiazolyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, oxadiazolyl, 15 triazolyl, thiadiazolyl, pyranyl, pyridyl, piperidinyl, dioxanyl, morpholino, dithianyl, thiomorpholino, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, sulfolanyl, tetrazolyl, triazinyl, azepinyl, oxazepinyl, thiazepinyl, diazepinyl and thiazolinyl. In addition, the term heterocyclyl includes fused heterocyclyl groups, for example benzimidazolyl, 20 benzoxazolyl, imidazopyridinyl, benzoxazinyl, benzothiazinyl, oxazolopyridinyl, benzofuranyl, quinolinyl, quinazolinyl, quinoxalinyl, dihydroquinazolinyl, benzothiazolyl, phthalimido, benzofuranyl, benzodiazepinyl, indolyl and isoindolyl. The term heterocyclic should be similarly construed.

Halo means fluoro, chloro, bromo or iodo.

25 For the avoidance of doubt, unless otherwise indicated, the term substituted means substituted by one or more defined groups. In the case where groups may be selected from a number of alternatives groups, the selected groups may be the same or different.

For the avoidance of doubt, the term independently means that where more than one 30 substituent is selected from a number of possible substituents, those substituents may be the same or different.

35 The pharmaceutically or veterinarily acceptable salts of the compounds of formula I which contain a basic centre are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, with carboxylic acids or with organo-sulfonic acids. Examples include the HCl, HBr,

HI, sulfate or bisulfate, nitrate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, saccharate, fumarate, maleate, lactate, citrate, tartrate, gluconate, camsylate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate salts. Compounds of the invention can also provide pharmaceutically or veterinarilly acceptable metal salts, in particular non-toxic alkali and alkaline earth metal salts, with bases. Examples include the sodium, potassium, aluminium, calcium, magnesium, zinc, diolamine, clamine, ethylenediamine, tromethamine, chloine, megulamine and diethanolamine salts. For reviews on suitable pharmaceutical salts see Berge *et al*, J. Pharm, Sci., 66, 1-19, 1977; P L Gould, International Journal of Pharmaceutics, 33 (1986), 201-217; and Bighley *et al*, Encyclopedia of Pharmaceutical Technology, Marcel Dekker Inc, New York 1996, Volume 13, page 453-497.

Hereinafter, the compounds, their pharmaceutically acceptable salts, their solvates and polymorphs, defined in any aspect of the invention or preferred embodiment (except intermediate compounds in chemical processes) are referred to as "compounds of the invention".

The pharmaceutically acceptable solvates of the compounds of the invention include hydrates thereof.

The compounds of the invention and intermediates may possess one or more chiral centres and so exist in a number of stereoisomeric forms. All stereoisomers and mixtures thereof are included in the scope of the present invention.

Individual enantiomers may be obtained by a variety of techniques known to the skilled chemist, such as by high pressure liquid chromatography (HPLC) of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active base, as appropriate. A preferred optically active base is pseudoephedrine (see Preparation 69).

Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C.

The compounds of the invention may exist in one or more tautomeric forms. All tautomers and mixtures thereof are included within the scope of the present invention.

For example, a claim to 2-hydroxypyridinyl would also cover its tautomeric form, α -pyridonyl.

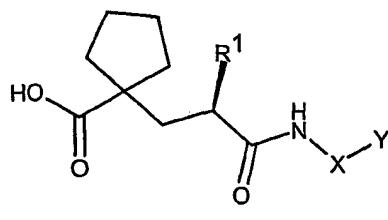
It will be appreciated by those skilled in the art that certain protected derivatives of 5 compounds of the invention, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". Further, certain compounds of the invention may act 10 as prodrugs of other compounds of the invention.

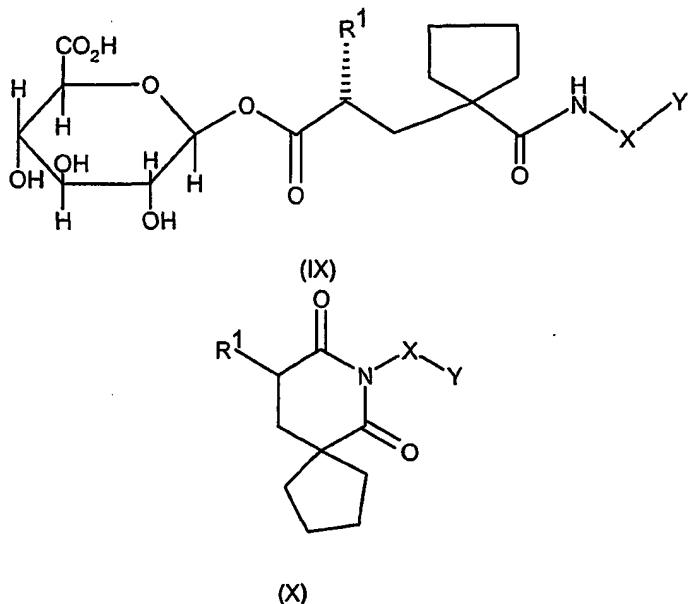
All protected derivatives and prodrugs of compounds of the invention are included within the scope of the invention. Examples of suitable pro-drugs for the compounds of the present invention are described in Drugs of Today, Volume 19, Number 9, 1983, pp 499 – 15 538 and in Topics in Chemistry, Chapter 31, pp 306 – 316 and in "Design of Prodrugs" by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference).

It will further be appreciated by those skilled in the art, that certain moieties, known to 20 those skilled in the art as "pro-moieties", for example as described by H. Bundgaard in "Design of Prodrugs" (the disclosure in which document is incorporated herein by reference) may be placed on appropriate functionalities when such functionalities are present within the compounds of the invention.

25 Preferred prodrugs for compounds of the invention include: esters, carbonate esters, hemiesters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides, carbamates, azo-compounds, phosphamides, glycosides, ethers, acetals and ketals.

Drug metabolism studies have shown that *in vivo*, compounds of formula I may form the 30 following compounds, which compounds also are inhibitors of NEP





These metabolites are formed in particular when R¹ is methoxyethyl and -XY is 3-(4-chlorophenyl)propyl.

The invention also includes all suitable isotopic variations of the compounds of the invention. An isotopic variation is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine and chlorine such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. Certain isotopic variations of the invention, for example, those in which a radioactive isotope such as ^3H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e. ^3H , and carbon-14, i.e. ^{14}C isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e. ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the compounds of the invention can generally be prepared by conventional procedures such as by the methods or preparations described in the Examples and Preparations hereafter using appropriate isotopic variations of suitable reagents.

25 The compounds of the invention are inhibitors of the zinc-dependent, neutral
endopeptidase EC.3.4.24.11., and it is proposed that the compounds of the invention will

treat the disease states listed below. This enzyme is involved in the breakdown of several bioactive oligopeptides, cleaving peptide bonds on the amino side of hydrophobic amino acid residues. The peptides metabolised include atrial natriuretic peptides (ANP), bombesin, bradykinin, calcitonin gene-related peptide, endothelins, 5 enkephalins, neuropeptides, substance P and vasoactive intestinal peptide. Some of these peptides have potent vasodilatory and neurohormone functions, diuretic and natriuretic activity or mediate behaviour effects.

Thus, the compounds of the invention, by inhibiting the neutral endopeptidase 10 EC.3.4.24.11, can potentiate the biological effects of bioactive peptides. Thus, in particular the compounds have utility in the treatment of a number of disorders, including hypertension, pulmonary hypertension, peripheral vascular disease, heart failure, angina, renal insufficiency, acute renal failure, cyclical oedema, Menière's disease, hyperaldosteronism (primary and secondary) and hypercalciuria. In addition, because 15 of their ability to potentiate the effects of ANF the compounds have utility in the treatment of glaucoma. As a further result of their ability to inhibit the neutral endopeptidase E.C.3.4.24.11 the compounds of the invention may have activity in other therapeutic areas including for example the treatment of menstrual disorders, preterm labour, pre-eclampsia, endometriosis, and reproductive disorders (especially male and 20 female infertility, polycystic ovarian syndrome, implantation failure). Also the compounds of the invention should treat asthma, inflammation, leukemia, pain, epilepsy, affective disorders, dementia and geriatric confusion, obesity and gastrointestinal disorders (especially diarrhoea and irritable bowel syndrome), wound healing (especially diabetic and venous ulcers and pressure sores), septic shock, the modulation of gastric acid 25 secretion, the treatment of hyperreninaemia, cystic fibrosis, restenosis, diabetic complications and atherosclerosis. In a preferred embodiment the compounds of the invention are useful in the treatment of male and female sexual dysfunction.

The compounds of the invention are particularly beneficial for the treatment of FSD 30 (especially FSAD) and male sexual dysfunction (especially male erectile dysfunction (MED)).

In accordance with the invention, FSD can be defined as the difficulty or inability of a woman to find satisfaction in sexual expression. FSD is a collective term for several 35 diverse female sexual disorders (Leiblum, S.R. (1998). Definition and classification of female sexual disorders. *Int. J. Impotence Res.*, 10, S104-S106; , Berman, J.R.,

Berman, L. & Goldstein, I. (1999). Female sexual dysfunction: Incidence, pathophysiology, evaluations and treatment options. *Urology*, 54, 385-391). The woman may have lack of desire, difficulty with arousal or orgasm, pain with intercourse or a combination of these problems. Several types of disease, medications, injuries or 5 psychological problems can cause FSD. Treatments in development are targeted to treat specific subtypes of FSD, predominantly desire and arousal disorders.

The categories of FSD are best defined by contrasting them to the phases of normal female sexual response: desire, arousal and orgasm (Leiblum, S.R. (1998). Definition 10 and classification of female sexual disorders. *Int. J. Impotence Res.*, 10, S104-S106). Desire or libido is the drive for sexual expression. Its manifestations often include sexual thoughts either when in the company of an interested partner or when exposed to other erotic stimuli. Arousal is the vascular response to sexual stimulation, an important component of which is genital engorgement and includes increased vaginal lubrication, 15 elongation of the vagina and increased genital sensation/sensitivity. Orgasm is the release of sexual tension that has culminated during arousal.

Hence, FSD occurs when a woman has an inadequate or unsatisfactory response in any 20 of these phases, usually desire, arousal or orgasm. FSD categories include hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorders and sexual pain disorders. Although the compounds of the invention will improve the genital response to sexual stimulation (as in female sexual arousal disorder), in doing so it may also improve the associated pain, distress and discomfort associated with intercourse and so treat other female sexual disorders.

25 Hypoactive sexual desire disorder is present if a woman has no or little desire to be sexual, and has no or few sexual thoughts or fantasies. This type of FSD can be caused by low testosterone levels, due either to natural menopause or to surgical menopause. Other causes include illness, medications, fatigue, depression and anxiety.

30 Female sexual arousal disorder (FSAD) is characterised by inadequate genital response to sexual stimulation. The genitalia do not undergo the engorgement that characterises normal sexual arousal. The vaginal walls are poorly lubricated, so that intercourse is painful. Orgasms may be impeded. Arousal disorder can be caused by reduced 35 oestrogen at menopause or after childbirth and during lactation, as well as by illnesses, with vascular components such as diabetes and atherosclerosis. Other causes result

from treatment with diuretics, antihistamines, antidepressants (e.g. SSRIs) or antihypertensive agents.

Sexual pain disorders (e.g. dyspareunia and vaginismus) is characterised by pain

5 resulting from penetration and may be caused by medications which reduce lubrication, endometriosis, pelvic inflammatory disease, inflammatory bowel disease or urinary tract problems.

The prevalence of FSD is difficult to gauge because the term covers several types of

10 problem, some of which are difficult to measure, and because the interest in treating FSD is relatively recent. Many women's sexual problems are associated either directly with the female ageing process or with chronic illnesses such as diabetes and hypertension.

15 Because FSD consists of several subtypes that express symptoms in separate phases of the sexual response cycle, there is not a single therapy. Current treatment of FSD focuses principally on psychological or relationship issues. Treatment of FSD is gradually evolving as more clinical and basic science studies are dedicated to the investigation of this medical problem. Female sexual complaints are not all

20 psychological in pathophysiology, especially for those individuals who may have a component of vasculogenic dysfunction (eg FSAD) contributing to the overall female sexual complaint. There are at present no drugs licensed for the treatment of FSD. Empirical drug therapy includes oestrogen administration (topically or as hormone replacement therapy), androgens or mood-altering drugs such as buspirone or

25 trazodone. These treatment options are often unsatisfactory due to low efficacy or unacceptable side effects.

Since interest is relatively recent in treating FSD pharmacologically, therapy consists of the following:- psychological counselling, over-the-counter sexual lubricants, and

30 investigational candidates, including drugs approved for other conditions. These medications consist of hormonal agents, either testosterone or combinations of oestrogen and testosterone and more recently vascular drugs, that have proved effective in male erectile dysfunction. None of these agents has been demonstrated to be very effective in treating FSD.

The Diagnostic and Statistical Manual (DSM) IV of the American Psychiatric Association defines Female Sexual Arousal Disorder (FSAD) as being: "a persistent or recurrent inability to attain or to maintain until completion of the sexual activity adequate lubrication-swelling response of sexual excitement. The disturbance must cause marked 5 distress or interpersonal difficulty."

The arousal response consists of vasocongestion in the pelvis, vaginal lubrication and expansion and swelling of the external genitalia. The disturbance causes marked distress and/or interpersonal difficulty.

10

FSAD is a highly prevalent sexual disorder affecting pre-, peri- and post menopausal (\pm HRT) women. It is associated with concomitant disorders such as depression, cardiovascular diseases, diabetes and UG disorders.

15 The primary consequences of FSAD are lack of engorgement/swelling, lack of lubrication and lack of pleasurable genital sensation. The secondary consequences of FSAD are reduced sexual desire, pain during intercourse and difficulty in achieving an orgasm.

20 It has recently been hypothesised that there is a vascular basis for at least a proportion of patients with symptoms of FSAD (Goldstein *et al.*, Int. J. Impot. Res., 10, S84-S90, 1998) with animal data supporting this view (Park *et al.*, Int. J. Impot. Res., 9, 27-37, 1997).

25 Drug candidates for treating FSAD, which are under investigation for efficacy, are primarily erectile dysfunction therapies that promote circulation to the male genitalia. They consist of two types of formulation, oral or sublingual medications (Apomorphine, Phentolamine, phosphodiesterase type 5 (PDE5) inhibitors e.g. Sildenafil), and prostaglandin (PGE₁) that are injected or administered transurethrally in men, and 30 topically to the genitalia in women.

The compounds of the invention are advantageous by providing a means for restoring a normal sexual arousal response - namely increased genital blood flow leading to vaginal, clitoral and labial engorgement. This will result in increased vaginal lubrication *via* 35 plasma transudation, increased vaginal compliance and increased genital sensitivity.

Hence, the compounds of the invention provide means to restore, or potentiate, the normal sexual arousal response.

Without being bound by theory, we believe that neuropeptides such as vasoactive 5 intestinal peptide (VIP) are major neurotransmitter candidates in the control of the female sexual arousal response, especially in the control of genital blood flow. VIP and other neuropeptides are degraded/ metabolised by NEP EC3.4.24.11. Thus, NEP inhibitors will potentiate the endogenous vasorelaxant effect of VIP released during arousal. This will lead to a treatment of FSAD, such as through enhanced genital blood 10 flow and hence genital engorgement. We have shown that selective inhibitors of NEP EC 3.4.24.11 enhance pelvic nerve-stimulated and VIP-induced increases in vaginal and clitoral blood flow. In addition, selective NEP inhibitors enhance VIP and nerve-mediated relaxations of isolated vagina wall.

15 Thus the present invention is advantageous as it helps provide a means for restoring a normal sexual arousal response - namely increased genital blood flow leading to vaginal, clitoral and labial engorgement. This will result in increased vaginal lubrication *via* plasma transudation, increased vaginal compliance and increased vaginal sensitivity. Hence, the present invention provides a means to restore, or potentiate the normal 20 sexual arousal response.

Male sexual dysfunction includes male erectile dysfunction, ejaculatory disorders such as premature ejaculation (PE), anorgasmia (inability to achieve orgasm) and desire disorders such as hypoactive sexual desire disorder (lack of interest in sex).

25 It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

30 The compounds of the invention find application in the following sub-populations of patients with FSD: the young, the elderly, pre-menopausal, peri-menopausal, post-menopausal women with or without hormone replacement therapy.

The compounds of the invention find application in patients with FSD arising from:-

i) Vasculogenic etiologies eg cardiovascular or atherosclerotic diseases, 35 hypercholesterolemia, cigarette smoking, diabetes, hypertension, radiation and perineal trauma, traumatic injury to the iliohypogastric pudendal vascular system.

- ii) Neurogenic etiologies such as spinal cord injuries or diseases of the central nervous system including multiple sclerosis, diabetes, Parkinsonism, cerebrovascular accidents, peripheral neuropathies, trauma or radical pelvic surgery.
- 5 5 iii) Hormonal/endocrine etiologies such as dysfunction of the hypothalamic/pituitary/gonadal axis, or dysfunction of the ovaries, dysfunction of the pancreas, surgical or medical castration, androgen deficiency, high circulating levels of prolactin eg hyperprolactinemia, natural menopause, premature ovarian failure, hyper and hypothyroidism.
- 10 10 iv) Psychogenic etiologies such as depression, obsessive compulsive disorder, anxiety disorder, postnatal depression/"Baby Blues", emotional and relational issues, performance anxiety, marital discord, dysfunctional attitudes, sexual phobias, religious inhibition or a traumatic past experiences.
- 15 15 v) Drug-induced sexual dysfunction resulting from therapy with selective serotonin reuptake inhibitors (SSRIs) and other antidepressant therapies (tricyclics and major tranquilizers), anti-hypertensive therapies, sympatholytic drugs, chronic oral contraceptive pill therapy.

20 Patients with mild to moderate MED should benefit from treatment with a compound of the invention and patients with severe MED may also respond. However, early investigations suggest that the responder rate of patients with mild, moderate and severe MED will be greater in combination with a PDE5 inhibitor. Mild, moderate and severe MED will be terms known to the man skilled in the art, but guidance can be found in *The Journal of Urology*, vol 151, 54-61 (Jan 1994).

25 The compounds of the invention find application in the following sub-populations of patients with MED: psychogenic, endocrinologic, neurogenic, arteriogenic, drug-induced sexual dysfunction (lactogenic) and sexual dysfunction related to cavernosal factors, particularly venogenic causes. These patient groups are described in more detail in 30 Clinical Andrology vol 23,no.4, p773-782, and chapter 3 of the book by I. Eardley and K. Sethia "Erectile Dysfunction - Current Investigation and Management, published by Mosby-Wolfe.

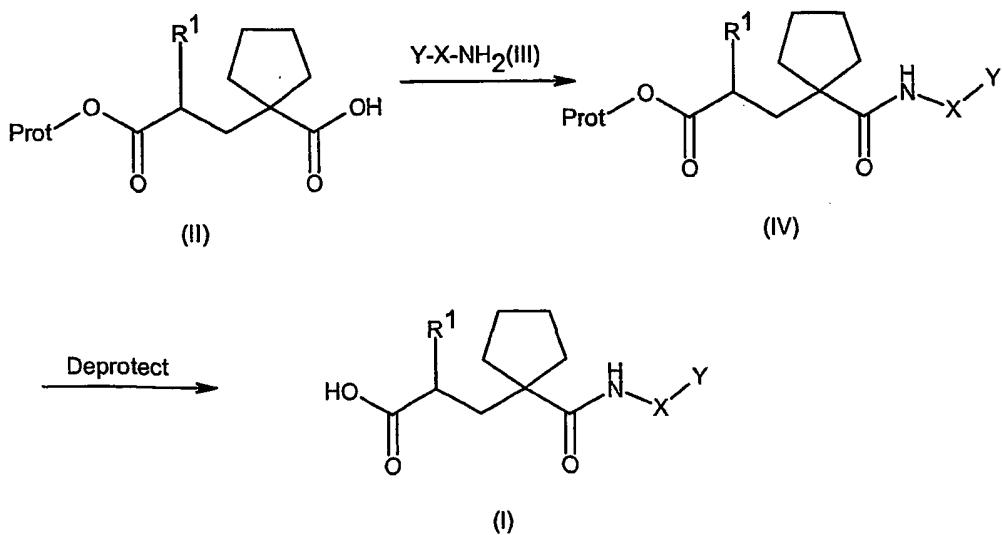
35 Compounds of the invention may be prepared in known manner in a variety of ways. In the following reaction schemes and hereafter, unless otherwise stated, R¹, n, X and Y are as defined in the first aspect. These processes form further aspects of the invention.

Throughout the specification, general formulae are designated by Roman numerals I, II, III, IV etc. Subsets of these general formulae are defined as Ia, Ib, Ic etc, IVa, IVb, IVc etc.

5

Compounds of general formula I may be prepared by reacting a compound of formula II (where Prot is a suitable protecting group) with an amine of formula III to give compounds of formula IV followed by deprotection (see Scheme 1). Preferred reaction conditions for the acid/amine coupling step comprise reacting II with III (or its amine salt) in the presence of an activating agent, optionally a catalyst, and an excess of an acid acceptor, in a suitable solvent. Particularly preferred reaction conditions comprise reacting II (1-1.5 equivalents), III (or its salt 1-1.5 equivalents), in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSCDI) or N,N'-dicyclohexylcarbodiimide (DCC) (1.1-1.3 equivalents), 1-hydroxybenzotrazole hydrate (HOBT) or dimethylaminopyridine (DMAP) (1.05-1.2 equivalents), N-methyl morpholine (NMM) or triethylamine (2.3-3 equivalents), in dimethylformamide or dichloromethane at between room temperature and 90°C for 16-18 hours.

Further particularly preferred reaction conditions comprise reacting II (1-1.5 equivalents) and 1,1'-carbonyldiimidazole (1-1.5 equivalents) in a suitable solvent (such as tetrahydrofuran, isopropylacetate or toluene) followed by addition of III (or its amine salt in which case an organic base such as triethylamine or Hunig's base is present) at a reaction temperature between room temperature and 90°C.

25 Scheme 1

Alternatively, the acid/amine coupling step may be performed via the acid chloride in the presence of an excess of acid acceptor, in a suitable solvent. The acid chloride may be isolated or it may be generated *in situ*. Preferred reaction conditions comprise reacting the acid chloride of II (1-1.1 equivalents), III (or its salt, 1 to 1.5 equivalents),

5 triethylamine or *N*-methyl morpholine (1.4-10 equivalents), in dichloromethane at room temperature for 24 hours. Compounds of formula II can be converted to the acid chloride *in situ* by treatment with oxalyl chloride in dichloromethane in the presence of a catalytic amount of dimethylformamide for 2 hours at room temperature.

10 Methods for deprotection of an acid group depend on the protecting group. For examples of protection/deprotection methodology see "Protective groups in Organic synthesis", TW Greene and PGM Wutz.

For example, when Prot is a *tert*-butyl, deprotection conditions comprise reacting IV with

15 trifluoroacetic acid/dichloromethane (1:1-2.5 by volume), at room temperature for 2-18 hours, optionally in the presence of a carbocation scavenger, e.g. anisole (10 equivalents). When X or Y contains a hydroxy group, base hydrolysis of the intermediate trifluoroacetic acid ester may be necessary. Alternative methodology for deprotection when Prot is *tert*-butyl comprises treating IV with hydrochloric acid in dichloromethane at

20 room temperature for 3 hours. For the avoidance of doubt, Prot as *tert*-butyl is given by way of example and is not intended to be limited to *tert*-butyl.

The process according to Scheme 1 forms a further aspect of the invention.

25 Intermediates of general formula IV are novel. Therefore according to a further aspect, the invention provides a compound of formula IV.

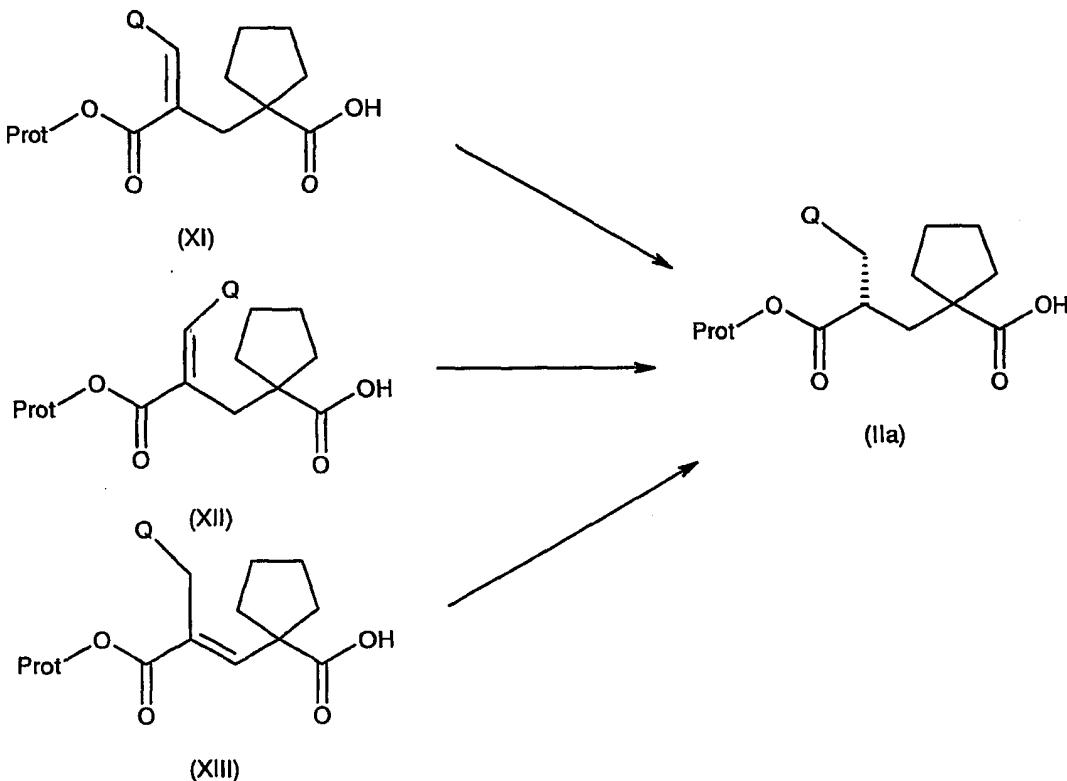
A number of compounds of formula II are known in the art (see EP274234-B1 and WO9113054). Other compounds of formula II can be prepared in analogous fashion.

30 Compounds of general formula I and II, where R¹ is not hydrogen, possess a chiral centre at the carbon attached to R¹. Individual enantiomers may be obtained by a variety of methods known to the skilled chemists, such as from a corresponding optically pure intermediate or via resolution. A preferred method of resolution is via the (+)-

35 pseudoephedrine salt (see WO9113054, Example 10 therein).

Alternatively compounds of formula IIa, i.e. chiral compounds of formula II where R¹ is optionally substituted C₁₋₆alkyl (where Q is the substituent on the C₁₋₆alkyl group defined for R¹ in the first aspect), may be prepared by asymmetric hydrogenation of compounds of formula XI, XII, or XIII according to reaction scheme 1a.

5

Scheme 1a

Typical hydrogenating conditions comprise treating compounds of formula XI, XII or XIII [or an organic or inorganic salt (eg sodium salt) thereof] with a suitable asymmetric hydrogenation catalyst under elevated hydrogen pressure in a suitable solvent. Preferred catalysts contain one or more chiral ligands, preferably chiral phosphine ligands, coordinated to a suitable transition metal (for example rhodium, ruthenium, iridium, palladium). Preferred catalysts are:

15 [(R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthylchloro(*para*-cymene)] ruthenium chloride (*J. Org. Chem.* 1994, 59, 3064-76);

[(S)-3,3',4,4',5,5'-hexamethyl(6,6'-diphenyl)-2,2'-diyl]bis(diphenylphosphino)ruthenium bis(trifluoroacetate) (see WO 01/94359);

[(R)-(-)-4,12-bis(diisopropylphosphino)-[2.2]-paracyclophano-(1,5-cyclooctadiene)] rhodium (I) tetrafluoroborate (*J. Am. Chem. Soc.* 1997, 119, 6207-6208);

20

[bis-((2S,5S)-2,5-dimethyl-1-phenylphospholano)(1,5-cyclooctadiene)] rhodium (I) tetrafluoroborate (*Tetrahedron: Asymm.*, 1991, 2, 569-92); and
[(*R*)-(6,6'-dimethoxybiphenyl-2,2'-diyl)bis(diphenylphosphino)] ruthenium bis (trifluoroacetate) (EP398132).

5 Preferred reaction conditions comprise a hydrogen pressure of up to 150 psi and a reaction temperature between 0 and 100 °C (preferably 50 to 60 °C). Preferred solvents are protic, such as methanol or ethanol.

In scheme 1a, compound of formula (XIII) is the preferred starting material.

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The process of scheme 1a forms a further aspect of the invention.

Alternatively compounds of formula I and IV may be prepared directly by asymmetric hydrogenation of unsaturated compounds corresponding to XI, XII and XIII.

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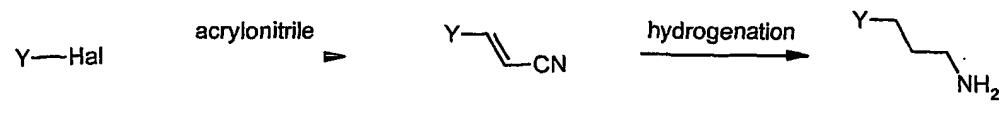
Compounds of formula IIIa, i.e. compounds of formula III where X is -(CH₂)₃-, may be prepared according to reaction Scheme 2. Firstly, compounds of formula V undergo the Heck reaction with acrylonitrile in the presence of a suitable catalyst system such as palladium and excess base such as triethylamine or 4-methylmorpholine to give

20 compounds of formula VI. Typical reaction conditions comprise 1.0-1.5 equivalents of the aryl halide, 3 equivalents of base, 0.1 equivalents of palladium catalyst (preferably palladium (II) acetate), 0.2 equivalents of phosphine ligand (preferably tri-*o*-tolylphosphine) in 1,4-dioxan, acetonitrile or DMF (preferably acetonitrile) at reflux.

Compounds of formula VI are then subjected to catalytic hydrogenation to give

25 compounds of formula IIIa. Typical hydrogenation conditions comprise treating VI with Raney nickel in ethanol or methanol at a pressure of 15 to 150 psig and 25 and 80°C. Preferably in ethanol at 30psig and 25°C.

Scheme 2



30 (V)

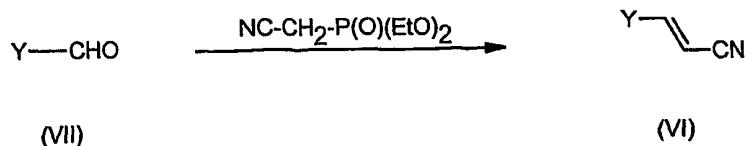
(VI)

(IIIa)

Alternatively compounds of formula VI may be prepared according to reaction scheme 3 by reacting compounds of formula VII with diethylcyanomethyl phosphonate. Typical reaction conditions comprise reacting diethylcyanomethyl phosphonate with a suitable

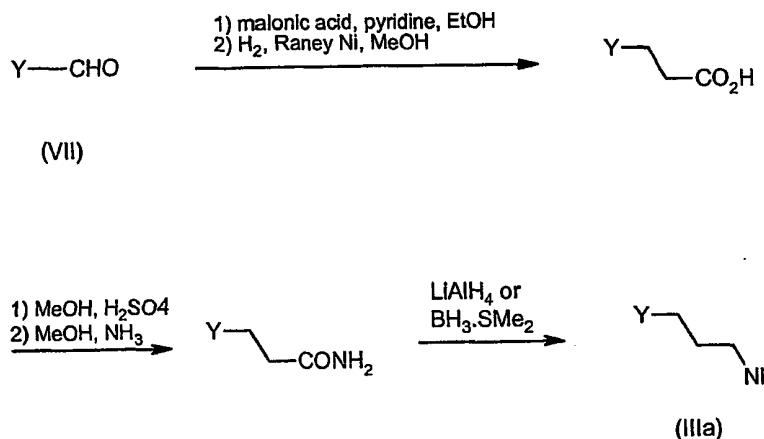
base (for example sodium hydride, lithium chloride/Hunigs base or sodium ethoxide) in a suitable solvent at room temperature (for example dichloromethane, tetrahydrofuran or diethyl ether) followed by addition of compound of formula VII.

5 Scheme 3



Alternatively compounds of formula IIIa may be prepared according to Scheme 4.

10 Scheme 4



Other compounds of formula (III), (V), (VI) and (VII) are either available from commercial sources; known in the prior art; or can be prepared from compounds known in the prior art by using methods known in the prior art or by using methods described herein (see

15 Examples and Preparations Sections).

All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional. Appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products 20 will be well-known to those skilled in the art with reference to literature precedents and the Examples and Preparations hereinbelow.

A pharmaceutically acceptable salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of the formula (I) and the desired 25 acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

The compounds of the invention [particularly (2S)-2-{{1-({{3-(4-chlorophenyl)propyl}amino} carbonyl)cyclopentyl}methyl}-4-methoxybutanoic acid (Example 22)] may be combined with one or more further active ingredients selected

5 from the list:

- 1) One or more naturally occurring or synthetic prostaglandins or esters thereof. Suitable prostaglandins for use herein include compounds such as alprostadil, prostaglandin E₁, prostaglandin E₀, 13, 14 - dihydroprosta glandin E₁, prostaglandin E₂, eprostolin, natural synthetic and semi-synthetic prostaglandins and derivatives thereof including those described in WO-00033825 and/or US 10 6,037,346 issued on 14th March 2000 all incorporated herein by reference, PGE₀, PGE₁, PGA₁, PGB₁, PGF₁ α , 19-hydroxy PGA₁, 19-hydroxy - PGB₁, PGE₂, PGB₂, 19-hydroxy-PGA₂, 19-hydroxy-PGB₂, PGE₃ α , carboprost tromethamine 15 dinoprost, tromethamine, dinoprostone, lipo prost, gemeprost, metenoprost, sulprostune, tiaprost and moxisylate.
- 2) One or more α - adrenergic receptor antagonist compounds also known as α - adrenoceptors or α -receptors or α -blockers. Suitable compounds for use herein include: the α -adrenergic receptor blockers as described in PCT application 20 WO99/30697 published on 14th June 1998, the disclosures of which relating to α -adrenergic receptors are incorporated herein by reference and include, selective α_1 -adrenoceptor or α_2 -adrenoceptor blockers and non-selective adrenoceptor blockers, suitable α_1 -adrenoceptor blockers include: phentolamine, phentolamine mesylate, trazodone, alfuzosin, indoramin, naftopidil, tamsulosin, dapiprazole, phenoxybenzamine, idazoxan, efaraxan, yohimbine, rauwolfa 25 alkaloids, Recordati 15/2739, SNAP 1069, SNAP 5089, RS17053, SL 89.0591, doxazosin, terazosin, abanoquil and prazosin; α_2 -blocker blockers from US 6,037,346 [14th March 2000] dibenarnine, tolazoline, trimazosin and dibenarnine; α -adrenergic receptors as described in US patents: 4,188,390; 4,026,894; 30 3,511,836; 4,315,007; 3,527,761; 3,997,666; 2,503,059; 4,703,063; 3,381,009; 4,252,721 and 2,599,000 each of which is incorporated herein by reference; α_2 - Adrenoceptor blockers include: clonidine, papaverine, papaverine hydrochloride, optionally in the presence of a cariotonic agent such as piroxamine.
- 3) One or more NO-donor (NO-agonist) compounds. Suitable NO-donor 35 compounds for use herein include organic nitrates, such as mono- di or tri-nitrates or organic nitrate esters including glycyl brinitrate (also known as nitroglycerin), isosorbide 5-mononitrate, isosorbide dinitrate, pentaerythritol

tetrinitrate, erythrityl tetranitrate, sodium nitroprusside (SNP), 3-morpholinosydnonimine molsidomine, S-nitroso- N-acetyl penicilliamine (SNAP) S-nitroso-N-glutathione (SNO-GLU), N-hydroxy - L-arginine, amylnitrate, linsidomine, linsidomine chlorohydrate, (SIN-1) S-nitroso - N-cysteine, diazenium diolates, (NONOates), 1,5-pentanedinitrate, L-arginene, ginseng, zizphi fructus, molsidomine, Re – 2047, nitrosylated maxislyte derivatives such as NMI-678-11 and NMI-937 as described in published PCT application WO 0012075.

5 4) One or more potassium channel openers or modulators. Suitable potassium channel openers/modulators for use herein include nicorandil, cromakalim, levromakalim, lemakalim, pinacidil, cliazoxide, minoxidil, charybdotoxin, glyburide, 4-amino pyridine, BaCl₂.

10 5) One or more dopaminergic agents, preferably apomorphine or a selective D₂, D₃ or D₂/D₃agonist such as, pramipexole and ropirinol (as claimed in WO-0023056), PNU95666 (as claimed in WO-0040226).

15 6) One or more vasodilator agents. Suitable vasodilator agents for use herein include nimodipine, pinacidil, cyclandelate, isoxsuprine, chloropromazine, halo peridol, Rec 15/2739, trazodone.

7) One or more thromboxane A2 agonists.

8) One or more CNS active agents.

20 9) One or more ergot alkaloids. Suitable ergot alkaloids are described in US patent 6,037,346 issued on 14th March 2000 and include acetergamine, brazergoline, bromerguride, cianergoline, delorgotile, disulergine, ergonovine maleate, ergotamine tartrate, etisulergine, lergotile, lysergide, mesulergine, metergoline, metergamine, nicergoline, pergolide, propisergide, proterguride, terguride.

25 10) One or more compounds which modulate the action of natriuretic factors in particular atrial natriuretic factor (also known as atrial natriuretic peptide), B type and C type natriuretic factors such as inhibitors or neutral endopeptidase.

11) One or more compounds which inhibit angiotensin-converting enzyme such as enapril, and combined inhibitors of angiotensin-converting enzyme and neutral endopeptidase such as omapatrilat.

30 12) One or more angiotensin receptor antagonists such as losartan.

13) One or more substrates for NO-synthase, such as L-arginine.

14) One or more calcium channel blockers such as amlodipine.

15) One or more antagonists of endothelin receptors and inhibitors or endothelin-converting enzyme.

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- 16) One or more cholesterol lowering agents such as statins (e.g. atorvastatin/ Lipitor- trade mark) and fibrates.
- 17) One or more antiplatelet and antithrombotic agents, e.g. tPA, uPA, warfarin, hirudin and other thrombin inhibitors, heparin, thromboplastin activating factor inhibitors.
- 5 18) One or more insulin sensitising agents such as rezulin and hypoglycaemic agents such as glipizide.
- 19) L-DOPA or carbidopa.
- 20) One or more acetylcholinesterase inhibitors such as donezilip.
- 10 21) One or more steroidal or non-steroidal anti-inflammatory agents.
- 22) One or more estrogen receptor modulators and/or estrogen agonists and/or estrogen antagonists, preferably raloxifene, tibolone or lasofoxifene, (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol and pharmaceutically acceptable salts thereof the preparation of which is detailed in WO 96/21656.
- 15 23) One or more modulators of cannabinoid receptors.
- 24) One or more of an NPY (neuropeptide Y) inhibitor, more particularly NPY1 or NPY5 inhibitor, preferably NPY1 inhibitor, preferably said NPY inhibitors (including NPY Y1 and NPY Y5) having an IC50 of less than 100nM , more preferably less than 50nM. An assay for identifying NPY inhibitors is presented in WO-A-98/52890 (see page 96, lines 2 to 28).
- 20 25) One or more of vasoactive intestinal protein (VIP), VIP mimetic, VIP analogue, more particularly mediated by one or more of the VIP receptor subtypes VPAC1,VPAC or PACAP (pituitary adenylate cyclase activating peptide), one or more of a VIP receptor agonist or a VIP analogue (eg Ro-125-1553) or a VIP fragment, one or more of a α -adrenoceptor antagonist with VIP combination (eg Invicorp, Aviptadil).
- 26) One or more of a melanocortin receptor agonist or modulator or melanocortin enhancer, such as melanotan II, PT-14, PT-141 or compounds claimed in WO-30 09964002, WO-00074679, WO-09955679, WO-00105401, WO-00058361, WO-00114879, WO-00113112, WO-09954358.
- 27) One or more of a serotonin receptor agonist, antagonist or modulator, more particularly agonists, antagonists or modulators for 5HT1A (including VML 670), 5HT2A, 5HT2C, 5HT3 and/or 5HT6 receptors, including those described in WO-35 09902159, WO-00002550 and/or WO-00028993.

28) one or more of an androgen such as androsterone, dehydro-androsterone, testosterone, androstenedione and a synthetic androgen.

29) one or more of an oestrogen, such as oestradiol, oestrone, oestriol and a synthetic estrogen, such as oestrogen benzoate.

5 30) One or more of a modulator of transporters for noradrenaline, dopamine and/or serotonin, such as bupropion, GW-320659.

31) One or more of a purinergic receptor agonist and/or modulator.

32) One or more of a neurokinin (NK) receptor antagonist, including those described in WO-09964008.

10 33) One or more of an opioid receptor agonist, antagonist or modulator, preferably agonists for the ORL-1 receptor.

34) One or more of an agonist or modulator for oxytocin/vasopressin receptors, preferably a selective oxytocin agonist or modulator.

35) One or more of a PDE inhibitor, more particularly a PDE 2, 3, 4, 5, 7 or 8 inhibitor, preferably PDE2 or PDE5 inhibitor and most preferably a PDE5 inhibitor (see hereinafter), said inhibitors preferably having an IC₅₀ against the respective enzyme of less than 100nM. Suitable cGMP PDE5 inhibitors for the use according to the present invention include:

20 the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in EP-A-0463756; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in EP-A-0526004; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 93/06104; the isomeric pyrazolo [3,4-d]pyrimidin-4-ones disclosed in published international patent application WO 93/07149; the quinazolin-4-ones disclosed in published international patent application WO 93/12095; the pyrido [3,2-d]pyrimidin-4-ones disclosed in published international patent application WO 94/05661; the purin-6-ones disclosed in published international patent application WO 94/00453; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 98/49166; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 99/54333; the pyrazolo [4,3-d]pyrimidin-4-ones disclosed in EP-A-0995751; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 00/24745; the pyrazolo [4,3-d]pyrimidin-4-ones disclosed in EP-A-0995750; the compounds disclosed in published international application WO95/19978; the compounds disclosed in published international application WO 99/24433 and the compounds disclosed in published international application WO 93/07124. The

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pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international application WO 01/27112; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international application WO 01/27113; the compounds disclosed in EP-A-1092718 and the compounds disclosed in EP-A-1092719.

5

Further suitable PDE5 inhibitors for the use according to the present invention include: 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil) also known as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulphonyl]-4-methylpiperazine (see EP-A-0463756); 5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see EP-A-0526004); 3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO98/49166); 3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO99/54333); (+)-3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1(R)-methylethoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, also known as 3-ethyl-5-[5-[4-ethylpiperazin-1-ylsulphonyl]-2-[(1R)-2-methoxy-1-methylethyl]oxy]pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one (see WO99/54333); 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, also known as 1-[6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-3-pyridylsulphonyl]-4-ethylpiperazine (see WO 01/27113, Example 8); 5-[2-*iso*-Butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(1-methylpiperidin-4-yl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO 01/27113, Example 15); 5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-phenyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO 01/27113, Example 66); 5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO 01/27112, Example 124); 5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO 01/27112, Example 132); (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (IC-351), i.e. the compound of examples 78 and 95 of published international application WO95/19978, as well as the compound of examples 1,

3, 7 and 8; 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil) also known as 1-[[3-(3,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f]-as-triazin-2-yl)-4-ethoxyphenyl]sulphonyl]-4-ethylpiperazine, i.e. the compound of examples 20, 5 19, 337 and 336 of published international application WO99/24433; and the compound of example 11 of published international application WO93/07124 (EISAI); and compounds 3 and 14 from Rotella D P, *J. Med. Chem.*, 2000, 43, 1257.

10 Still other suitable PDE5 inhibitors include: 4-bromo-5-(pyridylmethylamino)-6-[3-(4-chlorophenyl)-propoxy]-3(2H)pyridazinone; 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinoxolinyl]-4-piperidine-carboxylic acid, monosodium salt; (+)-cis-5,6a,7,9,9a-hexahydro-2-[4-(trifluoromethyl)-phenylmethyl]-5-methyl-cyclopent-4,5]imidazo[2,1-b]purin-4(3H)one; furazlocillin; 15 cis-2-hexyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]-imidazo[2,1-b]purin-4-one; 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylate; 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylate; 4-bromo-5-(3-pyridylmethylamino)-6-(3-(4-chlorophenyl) propoxy)-3- (2H)pyridazinone; 1-methyl-5(5-morpholinoacetyl-2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro- 7H-20 pyrazolo(4,3-d)pyrimidin-7-one; 1-[4-[(1,3-benzodioxol-5-ylmethyl)arnino]-6-chloro-2- quinazolinyl]-4-piperidinecarboxylic acid, monosodium salt; Pharmaprojects No. 4516 (Glaxo Wellcome); Pharmaprojects No. 5051 (Bayer); Pharmaprojects No. 5064 (Kyowa Hakko; see WO 96/26940); Pharmaprojects No. 5069 (Schering Plough); GF-196960 (Glaxo Wellcome); E-8010 and E-4010 25 (Eisai); Bay-38-3045 & 38-9456 (Bayer) and Sch-51866.

For treating FSD, the compounds of the invention [particularly (2S)-2-{{1-({{3-(4-chlorophenyl)propyl}amino} carbonyl)cyclopentyl}methyl}-4-methoxybutanoic acid (Example 22)] may preferably be combined with one or more active ingredients selected 30 from the list:

- a PDE5 inhibitor, more preferably 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil); (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl) -pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (IC-351); 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil); 5-[2-ethoxy-5-(4-

ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one and pharmaceutically acceptable salts thereof;

5 b) an NPY Y1 inhibitor;

 c) a dopamine agonist such as apomorphine or a selective D₂, D₃ or D₂/D₃agonist such as, pramipexole and ropirinol;

 d) a melanocortin receptor agonist or modulator or melanocortin enhancer, preferably melanotan II, PT-14, PT-141;

10 e) an agonist, antagonist or modulator for 5HT2C;

 f) an estrogen receptor modulator, estrogen agonists and/or estrogen antagonists, preferably raloxifene, tibolone or lasofoxifene;

 g) an androgen such as androsterone, dehydro-androsterone, testosterone, androstanedione and a synthetic androgen; and

15 h) an oestrogen, such as oestradiol, oestrone, oestriol and a synthetic estrogen, such as oestrogen benzoate.

For treating MED, the compounds of the invention [particularly (2S)-2-{{1-({[3-(4-chlorophenyl)propyl]amino} carbonyl)cyclopentyl)methyl}-4-methoxybutanoic acid (Example 22)] may preferably be combined with one or more active ingredients selected from the list:

20 a) a PDE5 inhibitor, more preferably 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil); (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (IC-351); 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil); 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one and pharmaceutically acceptable salts thereof;

25 b) an NPY Y1 inhibitor;

 c) a dopamine agonist (preferably apomorphine) or a selective D₂, D₃ or D₂/D₃agonist such as, pramipexole and ropirinol;

30 d) a melanocortin receptor agonist or modulator or melanocortin enhancer, preferably melanotan II, PT-14, PT-141; and

e) an agonist, antagonist or modulator for 5HT2C;

Particularly preferred combinations for treating FSD are (2S)-2-{{1-({[3-(4-chlorophenyl)propyl]amino} carbonyl)cyclopentyl)methyl}-4-methoxybutanoic acid

5 (Example 22) and one or more active ingredients selected from the list:
5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-
7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil);
(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl) -
pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (IC-351);
10 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-
imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil);
5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-
dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-
15 pyrazolo[4,3-d]pyrimidin-7-one;
apomorphine;
melanotan II;
PT-141;
lasofoxifene;
20 raloxifene;
tibolone;
an androgen such as androsterone, dehydro-androsterone, testosterone,
androstenedione and a synthetic androgen; and
an oestrogen, such as oestradiol, oestrone, oestriol and a synthetic estrogen, such as
25 oestrogen benzoate.

Particularly preferred combinations for treating MED are (2S)-2-{{1-({[3-(4-chlorophenyl)propyl]amino} carbonyl)cyclopentyl)methyl}-4-methoxybutanoic acid

(Example 22) and one or more active ingredients selected from the list:
30 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-
7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil);
(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl) -
pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (IC-351);
2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-
35 imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil);

5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5 apomorphine;
melanotan II; and
PT-141.

10 If a combination of active agents are administered, then they may be administered simultaneously, separately or sequentially.

The compounds of the invention can be administered alone but, in human therapy will generally be administered in admixture with a suitable pharmaceutical excipient diluent or carrier selected with regard to the intended route of administration and standard

15 pharmaceutical practice.

For example, the compounds of the invention, can be administered orally, buccally or sublingually in the form of tablets, capsules (including soft gel capsules), ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for

20 immediate-, delayed-, modified-, sustained-, dual-, controlled-release or pulsatile delivery applications. The compounds of the invention may also be administered via fast dispersing or fast dissolving dosage forms.

Modified release and pulsatile release dosage forms may contain excipients such as

25 those detailed for immediate release dosage forms together with additional excipients that act as release rate modifiers, these being coated on and/or included in the body of the device. Release rate modifiers include, but are not exclusively limited to, hydroxypropylmethyl cellulose, methyl cellulose, sodium carboxymethylcellulose, ethyl cellulose, cellulose acetate, polyethylene oxide, Xanthan gum, Carbomer, ammonio
30 methacrylate copolymer, hydrogenated castor oil, carnauba wax, paraffin wax, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, methacrylic acid copolymer and mixtures thereof. Modified release and pulsatile release dosage forms may contain one or a combination of release rate modifying excipients. Release rate modifying excipients may be present both within the dosage form i.e. within the matrix, and/or on
35 the dosage form, i.e. upon the surface or coating.

Fast dispersing or dissolving dosage formulations (FDDFs) may contain the following ingredients: aspartame, acesulfame potassium, citric acid, croscarmellose sodium, crospovidone, diascorbic acid, ethyl acrylate, ethyl cellulose, gelatin, hydroxypropylmethyl cellulose, magnesium stearate, mannitol, methyl methacrylate, mint 5 flavouring, polyethylene glycol, fumed silica, silicon dioxide, sodium starch glycolate, sodium stearyl fumarate, sorbitol, xylitol. The terms dispersing or dissolving as used herein to describe FDDFs are dependent upon the solubility of the drug substance used, i.e. where the drug substance is insoluble a fast dispersing dosage form can be prepared and where the drug substance is soluble a fast dissolving dosage form can be 10 prepared.

The compositions of the invention may be administered by direct injection. The composition may be formulated for parenteral, mucosal, intramuscular, intravenous, subcutaneous, ocular, intraocular or transdermal administration. Depending upon the 15 need, the agent may be administered at a dose of from 0.01 to 30 mg/kg body weight, such as from 0.1 to 10 mg/kg, more preferably from 0.1 to 1 mg/kg body weight.

The term "administered" includes delivery by viral or non-viral techniques. Viral delivery mechanisms include but are not limited to adenoviral vectors, adeno-associated viral (AAV) 20 vectos, herpes viral vectors, retroviral vectors, lentiviral vectors, and baculoviral vectors. Non-viral delivery mechanisms include lipid mediated transfection, liposomes, immunoliposomes, lipofectin, cationic facial amphiphiles (CFAs) and combinations thereof. The routes for such delivery mechanisms include but are not limited to mucosal, nasal, oral, parenteral, gastrointestinal, topical, or sublingual routes.

25 In addition or in the alternative the compositions (or component parts thereof) of the present invention may be administered by direct injection. In addition or in the alternative the compositions (or component parts thereof) of the present invention may be administered topically (preferably to the genitalia). In addition or in the alternative the 30 compositions (or component parts thereof) of the present invention may be administered by inhalation. In addition or in the alternative the compositions (or component parts thereof) of the present invention may also be administered by one or more of: a mucosal route, for example, as a nasal spray or aerosol for inhalation or as an ingestable solution such as by an oral route, or by a parenteral route where delivery is by an injectable form, 35 such as, for example, by a rectal, ophthalmic (including intravitreal or intracameral), nasal, topical (including buccal and sublingual), intrauterine, vaginal or parenteral

(including subcutaneous, intraperitoneal, intramuscular, intravenous, intradermal, intracranial, intratracheal, and epidural) transdermal, intraperitoneal, intracranial, intracerebroventricular, intracerebral, intravaginal, intrauterine, or parenteral (e.g., intravenous, intraspinal, subcutaneous, transdermal or intramuscular) route.

5

By way of example, the pharmaceutical compositions of the invention may be administered in accordance with a regimen of 1 to 10 times per day, such as once or twice per day. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the individual undergoing therapy.

10 15 Hence, the term "administered" includes but is not limited to delivery by a mucosal route, for example, as a nasal spray or aerosol for inhalation or as an ingestable solution; a parenteral route where delivery is by an injectable form, such as, for example, an intravenous, intramuscular or subcutaneous route.

20 25 Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethyl cellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

30 Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the invention may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

35 The compounds of the invention can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly,

intraurethrally intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion techniques. In addition, they may be administered in the form of an implant. For such parenteral administration they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough

5 salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art. Parenteral formulations may be formulated for immediate-, delayed-, modified-, sustained-, dual-,

10 controlled-release or pulsatile delivery.

The following dosage levels and other dosage levels herein are for the average human subject having a weight range of about 65 to 70 kg. The skilled person will readily be able to determine the dosage levels required for a subject whose weight falls outside this

15 range, such as children and the elderly.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the invention or salts or solvates thereof will usually be from 10 to 1000 mg (in single or divided doses).

20 Thus, for example, tablets or capsules of the compounds of the invention or salts or solvates thereof may contain from 5 to 1000 mg, such as 5 to 500 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for

25 any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention. The skilled person will also appreciate that, in the treatment of certain conditions (including FSD and MED), compounds of the invention

30 may be taken as a single dose on an "as required" basis (i.e. as needed or desired).

The compounds of the invention can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray or nebuliser with the use of a

35 suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA

134A [trade mark] or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray or nebuliser may contain a solution or suspension of

5 the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

10 Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 1 to 50 mg of a compound of the invention for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 1 to 50 mg which may be administered in a single dose or, more usually, in divided doses

15 throughout the day.

Alternatively, compounds of the invention can be administered in the form of a suppository or pessary, or they may be applied topically (preferably to the genitalia) in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The

20 compounds of the invention may also be dermally administered. The compounds of the invention may also be transdermally administered, for example, by the use of a skin patch. They may also be administered by the ocular, pulmonary or rectal routes.

For ophthalmic use, compounds can be formulated as micronised suspensions in

25 isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

For application topically to the skin (preferably to the genitalia), compounds of the

30 invention can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a

35 mixture of one or more of the following: mineral oil, sorbitan monostearate, a

polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds of the invention may also be used in combination with a cyclodextrin.

5 Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be

10 used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

15 In a preferred embodiment, the compounds of the invention are delivered systemically (such as orally, buccally and sublingually), more preferably orally. Preferably such systemic (most preferably oral) administration is used to treat female sexual dysfunction, preferably FSAD.

20 Thus in a particularly preferred embodiment, there is provided the use of the compounds of the invention in the manufacture of a systemically delivered (preferably orally delivered) medicament for the treatment or prophylaxis of FSD, more preferably FSAD.

25 A preferred oral formulation uses immediate release tablets; or fast dispersing or dissolving dosage formulations (FDDFs).

In a further preferred embodiment, the compounds of the invention are administered topically, preferably directly to the female genitalia, especially the vagina.

30 Since NEP is present throughout the body, it is very unexpected that the compounds of the invention can be administered systemically and achieve a therapeutic response in the female genitalia without provoking intolerable (adverse) side effects. In EP 1 097 719-A1 and the animal model hereinafter, we have shown that NEP inhibitors administered to a rabbit model (*in vivo*) systemically increased genital blood flow, upon sexual arousal (mimiced by pelvic nerve stimulation) without adversely affecting

35 cardiovascular parameters, such as causing a significant hypotensive or hypertensive.

Preferably the compounds of the invention are administered for the treatment of FSD in the sexually stimulated patient (by sexual stimulation we mean to include visual, auditory or tactile stimulation). The stimulation can be before, after or during said administration.

5 Thus the compounds of the invention enhance the pathways/mechanisms that underlie sexual arousal in the female genitalia restoring or improving the sexual arousal response to sexual stimulation.

10 Thus a preferred embodiment provides the use of a compound of the invention in the preparation of a medicament for the treatment or prophylaxis of FSD in the stimulated patient.

15 For veterinary use, a compound of the invention, is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular animal.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention . "Active ingredient" means a compound of the invention.

20

Formulation 1: A tablet is prepared using the following ingredients:

| | weight/mg |
|-----------------------------|-----------|
| Active ingredient | 250 |
| Cellulose, microcrystalline | 400 |
| Silicon dioxide, fumed | 10 |
| Stearic acid | 5 |
| Total | 665 |

the components are blended and compressed to form tablets.

Formulation 2: An intravenous formulation may be prepared as follows:

| | |
|-------------------|---------|
| Active ingredient | 100mg |
| Isotonic saline | 1,000ml |

25

Typical formulations useful for administering the compounds of the invention topically to the genitalia are as follows:

Formualtion 3: A spray

Active ingredient (1.0%) in isopropanol (30%) and water.

Formulation 4: A foam

5 Active ingredient, acetic acid glacial, benzoic acid, cetyl alcohol, methyl parahydroxybenzoate, phosphoric acid, polyvinyl alcohol, propylene glycol, sodium carboxymethylcellulose, stearic acid, diethyl stearamide, van Dyke perfume No. 6301, purified water and isobutane.

10 **Formulation 5: A gel**

Active ingredient, docusate sodium BP, isopropyl alcohol BP, propylene glycol, sodium hydroxide, carbomer 934P, benzoic acid and purified water.

Formulation 6: A Cream

15 Active ingredient, benzoic acid, cetyl alcohol, lavender, compound 13091, methylparaben, propylparaben, propylene glycol, sodium carboxymethylcellulose, sodium lauryl sulfate, stearic acid, triethanolmine, acetic acid glacial, castor oil, potassium hydroxide, sorbic acid and purified water.

20 **Formulation 7: A pessary**

Active ingredient, cetomacrogol 1000 BP, citric acid, PEG 1500 and 1000 and purified water.

The invention additionally includes:

25 (i) A pharmaceutical composition including a compound of the invention, together with a pharmaceutically acceptable excipient, diluent or carrier.

(ii) A compound of the invention for use as a medicament.

(iii) The use of a compound of the invention as a medicament for treating or preventing a condition for which a beneficial therapeutic response can be obtained by the inhibition of neutral endopeptidase.

30 (iv) The use of a compound of the invention as a medicament for treating or preventing hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder or sexual pain disorder, preferably sexual arousal disorder, orgasmic disorder or sexual pain disorder, more preferably sexual arousal disorder.

35 (v) A method of treating FSD or MED in a mammal including treating said mammal with an effective amount of a compound of the invention.

- (vi) An FSD or MED treating pharmaceutical composition comprising a compound of the invention together with a pharmaceutically acceptable excipient, diluent or carrier.
- (vii) A compound of the invention for use in treating FSD or MED.
- 5 (viii) The use of a compound of the invention in the manufacture of a medicament for treating or preventing FSD or MED.

The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions are used:

10

| | |
|-----------------|---------------------------------------|
| Arbaccel® | filter agent |
| br | broad |
| Boc | <i>tert</i> -butoxycarbonyl |
| CDI | carbonyldiimidazole |
| δ | chemical shift |
| d | doublet |
| Δ | heat |
| DCCI | dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| DMA | dimethylacetamide |
| DMF | <i>N,N</i> -dimethylformamide |
| DMSO | dimethylsulfoxide |
| ES ⁺ | electrospray ionisation positive scan |
| ES ⁻ | electrospray ionisation negative scan |
| Ex | Example |
| h | hours |
| HOBt | 1-hydroxybenzotriazole |
| HPLC | high pressure liquid chromatography |
| m/z | mass spectrum peak |
| min | minutes |
| MS | mass spectrum |
| NMR | nuclear magnetic resonance |
| Prec | precursor |
| Prep | preparation |
| q | quartet |
| s | singlet |

| | |
|-----------------|---|
| t | triplet |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TS ⁺ | thermospray ionisation positive scan |
| WSCDI | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride |

¹H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The following abbreviations have been used for common solvents: CDCl₃, deuteriochloroform; DMSO, dimethylsulphoxide. The abbreviation psi means pounds per square inch and LRMS means low resolution mass spectrometry. Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel 60 F₂₅₄ plates, R_f is the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate. Melting points were determined using a Perkin Elmer DSC7 at a heating rate of 20°C/minute).

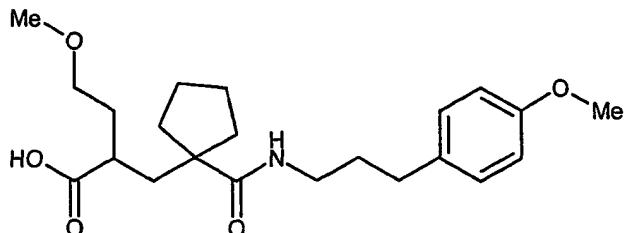
The powder X-ray diffraction (PXRD) pattern was determined using a SIEMENS D5000 powder X-ray diffractometer fitted with an automatic sample changer, a theta-theta goniometer, automatic beam divergence slits, a secondary monochromator and a scintillation counter. The sample was prepared for analysis by packing the powder on to a silicon wafer specimen mount. The specimen was rotated whilst being irradiated with copper K-alpha₁ X-rays (wavelength = 1.5406 Ångstroms) with the X-ray tube operated at 40kV/40mA. The analysis was performed with the goniometer running in step-scan mode set for a 5 second count per 0.02° step over a two theta range of 3° to 40°. In the results tables "Angle 2-Theta" is related to the interplanar spacing of the crystal, and the intensity is given as a percentage of the greatest peak (I/I₀).

The skilled crystallographer will appreciate that the relative intensities of the peaks may vary due to a number of factors such as orientation effects of crystals in the X-ray beam or the purity of the material being analysed or the degree of crystallinity of the sample. The peak positions may vary in sample height but the peak positions will remain substantially as tabulated. In addition, measurements using a different wavelength may result variation in the shift according to the Bragg equation - $n\lambda = 2d \sin \theta$. These

variations generated by use of alternative wavelengths are within the scope of the present invention.

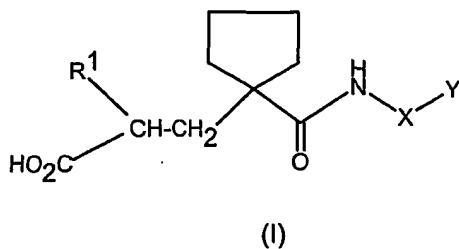
EXAMPLE 1

5 4-Methoxy-2-{[1-({[3-(4-methoxyphenyl)propyl]amino}carbonyl)cyclopentyl]-methyl}butanoic acid



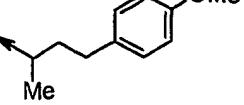
Hydrogen chloride gas was passed through a solution of the *tert*-butyl ester from preparation 1 (302mg, 0.72mmol) in dichloromethane (5 mL) at 0°C for 30 minutes. The 10 reaction mixture was concentrated *in vacuo* and the residue azeotroped with dichloromethane to give the title compound as a yellow oil, (233mg, 0.6mmol, 82%); ¹H NMR (CDCl₃ 400MHz) δ: 1.4-1.55 (m, 2H), 1.6-1.75 (m, 6H), 1.75-1.85 (m, 2H), 2.4-2.5 (m, 1H), 2.6 (t, 2H), 3.2 (s, 3H), 3.2-3.3 (m, 2H), 3.4 (t, 2H), 3.8 (s, 3H), 5.9 (t, 1H), 6.8 (d, 2H), 7.1 (d, 2H); LRMS: m/z 390 (M-H⁺); and HRMS m/z 392.2430 (C₂₂H₃₃NO₅ requires 392.2432).

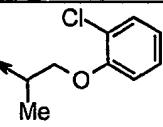
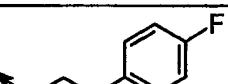
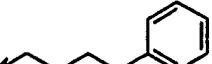
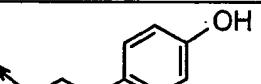
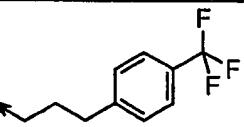
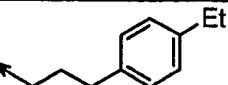
The following compounds of formula I (see Table 1) may be prepared by methods analogous to those of Example 1 from the *tert*-butyl ester precursor indicated.



20

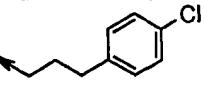
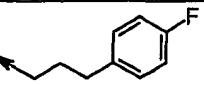
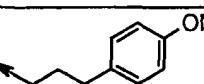
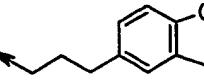
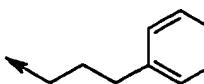
Table 1

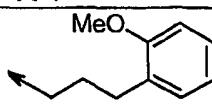
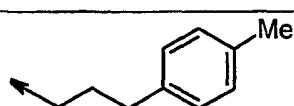
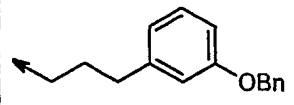
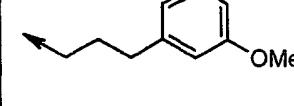
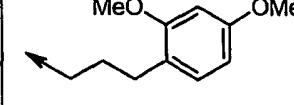
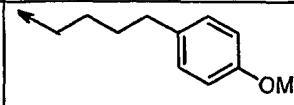
| Ex | Prec | R ¹ | -X-Y | Data |
|----|--------|----------------|---|---|
| 2 | Prep 2 | methoxy ethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.1 (t, 3H), 1.5 (m, 8H), 1.9 (m, 4H), 2.0 (m, 2H), 2.5 (m, 3H), 3.2 (s, 3H), 3.3 (m, 2H), 3.8 (t, 8H), 4.0 (s, 1H), 5.6 (d, 1H), 6.8 (d, 2H), 7.1 (d, 2H). LRMS: m/z 404 (M-H ⁺). |

| Ex | Prec | R ¹ | -X-Y | Data |
|----|--------|----------------|---|--|
| 3 | Prep 3 | methoxy ethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4 (d, 3H), 1.6 (m, 8H), 2.0 (m, 4H), 2.1 (dd, 1H), 2.5 (m, 1H), 3.2 (d, 3H), 3.4 (m, 2H), 4.0 (q, 2H), 4.4 (bs, 1H), 6.2 (m, 1H), 6.9 d, 2H), 7.2 (t, 1H), 7.4 (d, 1H). LRMS: m/z 410 (M-H ⁺). HRMS m/z 412.1885 (C ₂₁ H ₃₀ NO ₅ Cl requires 412.1813) |
| 4 | Prep 4 | methoxy ethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.5 (m, 2H), 1.6 (m, 4H), 1.8 (t, 2H), 1.9 (m, 2H), 2.0 (m, 2H), 2.4 (m, 1H), 3.2 (s, 4H), 3.3 (t, 2H), 6.0 (bs, 1H), 6.9 (t, 2H), 7.1 (t, 2H), 10.4 (bs, 1H). LRMS: m/z 379 (M-H ⁺). |
| 5 | Prep 5 | methoxy ethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4-1.6 (m, 10H), 1.8-2.0 (m, 4H), 2.4 (m, 1H), 2.6 (t, 2H), 3.2 (s, 4H), 3.3 (t, 2H), 3.3 (t, 2H), 5.9 (bs, 1H), 7.1 (m, 3H), 7.2 (t, 2H), 10.4 (bs, 1H). LRMS: m/z 374 (M-H ⁺). |
| 6 | Prep 6 | methoxy ethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.5-1.6 (m, 10H), 1.8 (m, 3H), 1.9 (m, 1H), 2.0 (q, 1H), 2.5 (m, 1H), 2.6 (t, 2H), 3.2 (m, 4H), 3.4 (q, 2H), 5.9 (bs, 1H), 7.1 (d, 3H), 7.3 (m, 2H). LRMS: m/z 362 (M+H ⁺). |
| 7 | Prep 7 | methoxy ethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.6 (m, 8H), 1.8 (m, 2H), 2.0 (m, 2H), 2.5 (m, 6H), 3.2 (s, 3H), 3.25 (m, 2H), 3.4 (m, 2H), 5.7 (bs, 1H), 6.7 (d, 2H), 7.0 (d, 2H). LRMS: m/z 376 (M-H ⁺). HRMS m/z 378.2288 (C ₂₁ H ₃₁ NO ₅ requires 378.2275) |
| 8 | Prep 8 | methoxy ethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.5-2.1 (m, 14H), 2.5 (m, 1H), 2.7 (m, 2H), 3.2 (s, 2H), 3.3 (m, 2H), 3.4 (m, 2H), 6.8 (s, 1H), 7.25 (d, 2H), 7.5 (d, 2H). LRMS: m/z 428 (M-H ⁺). HRMS m/z 430.2206 (C ₂₂ H ₃₀ NO ₄ F ₃ requires 430.2200) |
| 9 | Prep 9 | methoxy ethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.2 (m, 3H), 1.6 (m, 8H), 1.9 (m, 4H), 2.0 (m, 2H), 2.5 (m, 1H), 2.6 (m, 4H), 3.2 (s, 3H), 3.3 (m, 2H), 3.4 (m, 2H), 5.9 (bs, 1H), 7.0 (d, 4H). LRMS: m/z 388 (M-H ⁺). HRMS m/z 390.2639 (C ₂₃ H ₃₅ NO ₄ requires 390.2643) |

| Ex | Prec | R ¹ | -X-Y | Data |
|----|---------|----------------|------|---|
| 10 | Prep 10 | methoxy ethyl | | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.5-1.85 (m, 11H), 2.0-2.2 (m, 3H), 2.3 (s, 3H), 2.5 (m, 1H), 2.6 (t, 2H), 3.25 (s, 1H), 3.3 (s, 3H), 3.35-3.5 (m, 3H), 3.8 (s, 3H), 6.7-6.8 (m, 2H), 7.1 (d, 1H), 7.6 (s, 1H). MP 148-150°C. LRMS: m/z 406 (M+H ⁺). HRMS m/z 406.2597 (C ₂₃ H ₃₅ NO ₅ requires 406.2588). Anal. Found C, 67.71; H, 8.74; N, 3.41. C ₂₃ H ₃₄ NO ₅ ·0.15H ₂ O requires C, 67.67; H, 8.72; N, 3.43% |
| 11 | Prep 11 | methoxy ethyl | | ¹ H NMR (CDCl ₃ 400MHz) δ: 0.9 (t, 2H), 1.3 (m, 2H), 1.6 (m, 8H), 1.8 (m, 3H), 1.9 (m, 1H), 2.0 (dd, 1H), 2.4 (m, 1H), 2.6 (t, 2H), 3.2 (t, 2H), 3.3 (m, 5H), 3.4 (m, 1H), 4.5 (t, 2H), 5.9 (bs, 1H), 6.7 (d, 1H), 6.9 (d, 1H), 7.0 (bs, 1H). LRMS: m/z 404 (M+H ⁺). HRMS m/z 404.2434 (C ₂₃ H ₃₄ NO ₅ requires 404.2431) |
| 12 | Prep 12 | methoxy ethyl | | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.5-1.6 (m, 3H), 1.6-1.7 (m, 6H), 1.7-1.85 (m, 3H), 1.9-2.05 (m, 4H), 2.5-2.6 (m, 1H), 2.7 (t, 2H), 3.1-3.2 (m, 1H), 3.2-3.3 (t, 1H), 3.3 (s, 3H), 3.4-3.5 (m, 2H), 6.6 (bs, 1H), 6.7 (d, 1H), 6.8 (t, 1H), 7.0-7.1 (m, 2H). LRMS: m/z 376 (M+H ⁺) |
| 13 | Prep 13 | methoxy ethyl | | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.5-1.75 (m, 9H), 1.8-2.0 (m, 5H), 2.1 (dd, 1H), 2.5-2.6 (m, 1H), 2.6 (t, 2H), 3.25 (s, 3H), 3.25-3.3 (m, 2H), 3.35-3.4 (m, 2H), 5.9 (bs, 1H), 7.1 (d, 1H), 7.15-7.25 (m, 3H). LRMS: m/z 396 (M+H ⁺). HRMS m/z 396.1949 (C ₂₁ H ₃₁ NO ₄ Cl requires 396.1936) |
| 14 | Prep 14 | methoxy ethyl | | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.5-1.75 (m, 9H), 1.75-2.0 (m, 5H), 2.1 (dd, 1H), 2.45-2.55 (m, 1H), 2.75 (t, 2H), 3.25 (s, 3H), 3.20-3.3 (m, 2H), 3.35-3.4 (m, 2H), 6.1 (bs, 1H), 7.1-7.25 (m, 4H). LRMS: m/z 396 (M+H ⁺). HRMS m/z 396.1946 (C ₂₁ H ₃₁ NO ₄ Cl requires 396.1936) |

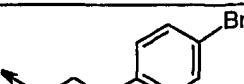
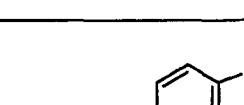
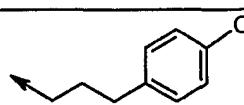
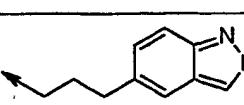
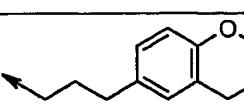
| Ex | Prec | R ¹ | -X-Y | Data |
|----|---------|----------------|------|---|
| 15 | Prep 15 | methoxy ethyl | | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.5-1.75 (m, 9H), 1.8-1.95 (m, 5H), 2.05 (dd, 1H), 2.4-2.5 (m, 1H), 2.6 (t, 2H), 3.25 (s, 3H), 3.20-3.3 (m, 2H), 3.35-3.4 (m, 2H), 6.1 (bs, 1H), 7.1 (d, 2H), 7.2 (d, 2H). LRMS: m/z 396 (M+H ⁺). HRMS m/z 396.1943 (C ₂₁ H ₃₁ NO ₄ Cl requires 396.1936) |
| 16 | Prep 16 | (R)-Pr | | ¹ H NMR (CDCl ₃ 400MHz) δ: 0.8 (t, 3H), 1.2-1.95 (m, 16H), 2.3 (m, 1H), 2.55 (m, 2H), 3.25 (m, 2H), 3.7 (s, 3H), 5.7 (s, 1H), 6.8 (d, 2H), 7.1 (d, 2H). LRMS: m/z 374 (M-H ⁺). HRMS m/z 376.2485 (C ₂₂ H ₃₅ NO ₄ requires 376.2482) |
| 17 | Prep 17 | (R)-Me | | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.18 (d, 3H), 1.45-1.96 (m, 11H), 2.08 (m, 1H), 2.41 (m, 1H), 2.59 (t, 2H), 3.3 (t, 2H), 3.8 (s, 3H), 5.67 (m, 1H), 6.82 (d, 2H), 7.08 (d, 2H). LRMS: m/z 348 (M+H ⁺). |
| 18 | Prep 18 | H | | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.47 (m, 2H), 1.73 (m, 4H), 1.77-2.00 (m, 6H), 2.31 (m, 2H), 2.60 (t, 2H), 3.29 (m, 2H), 3.8 (s, 3H), 5.57 (m, 1H), 6.82 (d, 2H), 7.11 (d, 2H). LRMS: m/z 334 (M+H ⁺). |
| 19 | Prep 19 | H | | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.47 (m, 2H), 1.73 (m, 4H), 1.77-2.00 (m, 6H), 2.31 (m, 2H), 2.60 (t, 2H), 3.29 (m, 2H), 3.8 (s, 3H), 5.57 (m, 1H), 6.82 (d, 2H), 7.11 (d, 2H). LRMS: m/z 338 (M+H ⁺). |
| 20 | Prep 20 | H | | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.40-1.98 (m, 12H), 2.37 (t, 2H), 2.58 (t, 2H), 3.23 (q, 2H), 5.57 (m, 1H), 7.07 (d, 2H), 7.20 (d, 2H). LRMS: m/z 338 (M+H ⁺). |
| 21 | Prep 21 | H | | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.46 (m, 2H), 1.66 (m, 4H), 1.73-1.98 (m, 6H), 2.29 (t, 2H), 2.58 (t, 2H), 3.17 (t, 2H), 3.26 (q, 2H), 4.53 (t, 2H), 6.59 (m, 1H), 6.70 (d, 1H), 6.90 (d, 1H), 7.01 (s, 1H). MP 94.5-97.0°C. LRMS: m/z 346 (M+H ⁺). Anal. Found C, 68.50; H, 7.78; N, 4.01. C ₂₀ H ₂₇ NO ₄ ·0.25H ₂ O requires C, 68.65; H, 7.92; N, 4.00% |

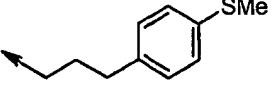
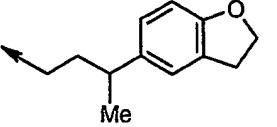
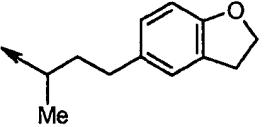
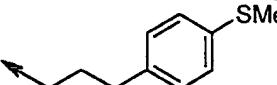
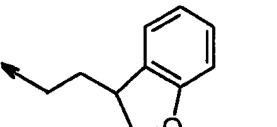
| Ex | Prec | R ¹ | -X-Y | Data |
|----|---------|------------------|---|---|
| 22 | Prep 22 | (S)-methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.5-1.7 (m, 9H), 1.75-1.95 (m, 5H), 2.05 (dd, 1H), 2.4-2.5 (m, 1H), 2.6 (t, 2H), 3.25 (s, 3H), 3.20-3.3 (m, 2H), 3.35-3.4 (m, 2H), 6.1 (bs, 1H), 7.1 (d, 2H), 7.2 (d, 2H). MP 75-77°C. LRMS: m/z 394 (M-H ⁺). |
| 23 | Prep 23 | (S)-methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4-2.1 (m, 14H), 2.45 (m, 1H), 2.55 (m, 2H), 3.2 (s, 3H), 3.25 (m, 2H), 3.35 (m, 2H), 5.9 (bs, 1H), 6.9 (m, 2H), 7.1 (m, 2H), 10.4 (bs, 1H). LRMS: m/z 378 (M-H ⁺). [α] _D +0.4 (EtOH, c 1). HRMS m/z 380.2232 (C ₂₂ H ₃₃ NO ₅ requires 380.2225). Anal. Found C, 63.73; H, 7.92; N, 4.11. C ₂₁ H ₃₀ NO ₄ F·0.67H ₂ O requires C, 63.62; H, 8.04; N, 3.82% |
| 24 | Prep 24 | (S)-methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4-1.70 (m, 8H), 1.80-2.05 (m, 6H), 2.4-2.5 (m, 1H), 2.6 (t, 2H), 3.2 (s, 3H), 3.2-3.3 (m, 2H), 3.4 (t, 2H), 3.8 (s, 3H), 5.8 (bs, 1H), 6.8 (d, 2H), 7.1 (d, 2H). LRMS: m/z 390 (M-H ⁺). [α] _D -0.01 (EtOH, c 1.87). HRMS m/z 392.2425 (C ₂₂ H ₃₃ NO ₅ requires 392.2432) |
| 25 | Prep 25 | (S)-methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.41-2.06 (m, 14H), 2.43-2.60 (m, 2H), 3.257 (t, 2H), 3.18 (t, 2H), 3.33 (s, 3H), 3.24-3.4 (m, 4H), 4.53 (t, 2H), 5.80 (bs, 1H), 6.66 (d, 1H), 6.88 (d, 1H), 7.0 (s, 1H). LRMS: m/z 402 (M-H ⁺). [α] _D 0.00 (EtOH, c 0.93). Anal. Found C, 66.85; H, 8.24; N, 3.35. C ₂₅ H ₃₅ NO ₅ ·0.5H ₂ O requires C, 66.97; H, 8.31; N, 3.40% |
| 26 | Prep 26 | H |  | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.13-1.98 (m, 10H), 2.16-2.28 (m, 4H), 2.70-3.03 (m, 4H), 5.60 (brs, 1H), 6.88 (d, 1H), 7.40 (d, 1H), 7.57 (d, 1H), 8.08 (d, 1H), 8.17 (d, 1H), 8.86 (d, 1H). LRMS: ES ⁻ m/z 353 (M-H ⁺). |

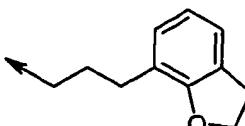
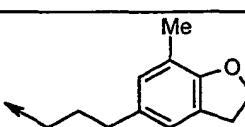
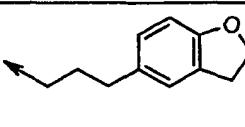
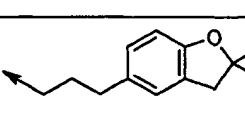
| Ex | Prec | R ¹ | -X-Y | Data |
|----|---------|-------------------|---|---|
| 27 | Prep 27 | methoxy ethyl |  | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.20 (m, 2H), 1.60 (m, 8H), 1.80 (t, 2H), 1.90 (m, 3H), 2.50 (m, 1H), 2.0 (t, 2H), 3.20 (m, 5H), 3.40 (m, 2H), 3.80 (s, 3H), 6.00 (brs, 1H), 6.90 (m, 2H), 7.10 (d, 2H), 7.20 (d, 2H). LRMS: ES+ m/z 392 (M+H). HRMS: m/z 392.2431 (C ₂₂ H ₃₃ NO ₅ requires 392.2422) |
| 28 | Prep 28 | methoxy ethyl |  | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.30 (m, 2H), 1.40-1.70 (m, 6H), 1.80 (m, 2H), 1.90-2.10 (m, 3H), 2.30 (s, 3H), 2.42 (m, 2H), 2.60 (t, 2H), 3.20 (s, 3H), 3.30 (m, 2H), 3.40 (m, 2H), 5.85 (brs, 1H), 7.15 (brs, 4H). LRMS: ES+ m/z 376 (M+H). HRMS m/z 376.2484 (C ₂₂ H ₃₃ NO ₄ requires 376.2483). |
| 29 | Prep 29 | methoxy ethyl |  | ¹ HNMR (CDCl ₃ , 400 MHz) δ: 1.60 (m, 8H), 1.90 (m, 4H), 2.00 (m, 2H), 2.50 (m, 1H), 2.60 (t, 2H), 3.20 (m, 5H), 3.30 (q, 2H), 5.00 (s, 2H), 5.80 (brs, 1H), 6.90 (m, 3H), 7.20 (t, 2H), 7.40 (m, 5H). LRMS: ES+ 468 (M+H). |
| 30 | Prep 30 | methoxy ethyl |  | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.43-1.76 (m, 10H), 1.80-2.15 (m, 4H), 2.50 (m, 1H), 2.60 (t, 2H), 3.25 (s, 3H), 3.30 (m, 2H), 3.35 (m, 2H), 3.78 (d, 2H), 4.01 (t, 1H), 5.75-5.95 (brm, 1H), 6.10-6.45 (brm, 1H), 6.70 (m, 1H), 6.90 (m, 1H), 7.18 (m, 1H). LRMS: ES+ 392.2 (M+H). |
| 31 | Prep 31 | methoxy ethyl |  | ¹ HNMR (CDCl ₃ , 400MHz) 1.50-1.70 (m, 8H), 2.00 (m, 3H), 2.10 (dd, 1H), 2.30 (m, 1H), 2.60 (t, 2H), 3.20 (m, 2H), 3.30 (s, 3H), 3.40 (q, 2H), 3.8 (d, 6H), 6.10 (brs, 1H), 6.30 (brd, 2H), 7.00 (d, 1H). LRMS: ES+ 422.3 (M+H). Anal. Found C 65.16; H 8.46; N 3.17 %. (C ₂₃ H ₃₅ NO ₆ Requires: C 65.53; H 8.36; N 3.32 %) |
| 32 | Prep 32 | (S)-methoxy ethyl |  | ¹ HNMR (CDCl ₃ , 300MHz) 1.50-1.78 (m, 12H), 1.91-2.13 (m, 4H), 1.48-1.62 (m, 3H), 3.20-3.47 (m, 7H), 3.80 (s, 3H), 5.82 (t, 1H), 6.83 (d, 2H), 7.10 (d, 2H). LRMS: TS ⁺ m/z 406 (M+H). |

| Ex | Prec | R ¹ | -X-Y | Data |
|----|---------|-------------------|------|--|
| 33 | Prep 33 | H | | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.40 (m, 2H), 1.55 (m, 4H), 1.80 (m, 4H), 1.90 (m, 2H), 2.2 (m, 2H), 3.1 (t, 2H), 3.3 (q, 2H), 5.60 (brs, 1H), 7.25 (m, 1H), 7.35 (m, 1H), 7.45 (m, 2H), 7.70 (d, 1H), 7.80 (d, 1H), 7.95 (d, 1H). LRMS: ES ⁻ m/z 352 (M-H), 705 (2M-H). |
| 34 | Prep 34 | H | | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.40 (m, 2H), 1.50 (m, 4H), 1.70-1.90 (m, 6H), 2.20 (m, 2H), 2.80 (t, 2H), 3.30 (q, 2H), 5.60 (brs, 1H), 7.25 (d, 1H), 7.40 (m, 2H), 7.55 (s, 1H), 7.70 (m, 3H). LRMS: ES ⁻ m/z 352 (M-H), 705 (2M-H). |
| 35 | Prep 35 | (S)-methoxy ethyl | | ¹ HNMR (CD ₃ OD, 300MHz) δ: 1.45-1.88 (m, 8H), 2.0-2.12 (m, 3H), 2.45 (c, 1H), 2.65 (t, 2H), 3.20 (t, 2H), 3.25 (s, 3H), 3.35 (t, 2H), 7.10-7.20 (m, 2H), 7.35 (d, 1H). LRMS: ES ⁻ m/z 412 (M-H). CHN: 0.15 CH ₂ Cl ₂ |
| 36 | Prep 36 | (S)-methoxy ethyl | | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.45-1.70 (m, 10H), 1.75-1.83 (m, 1H), 1.85-1.96 (m, 3H), 2.05-2.15 (m, 2H), 2.43-2.52 (m, 1H), 2.57 (t, 2H), 3.21 (s, 3H), 3.35 (bs, 2H), 5.80 (bs, 1H), 6.89 (d, 1H), 6.95 (d, 1H), 7.23-7.30 (m, 1H). LRMS: ES ⁺ m/z 436 (M+Na). Found: C, 59.36, 59.17; H, 7.30, 7.27; N, 2.68, 2.69. Requires: C, 58.96; H, 7.46; N, 3.03 (M + 0.29 pentane + 0.11 TFA + 0.80 water) |
| 37 | Prep 37 | (S)-methoxy ethyl | | ¹ HNMR (CD ₃ OD, 400MHz) δ: 1.25 (m, 1H), 1.40-1.82 (m, 11H), 2.0 (m, 3H), 2.38 (c, 1H), 2.60 (t, 2H), 3.08-3.18 (m, 7H), 5.46 (brs, 1H), 6.80 (d, 2H), 7.25 (s, 1H). LRMS: ES ⁻ m/z 396 (M-H). CHN: 0.36 CH ₂ Cl ₂ 0.6 H ₂ O |
| 38 | Prep 38 | H | | ¹ HNMR (CD ₃ OD, 400MHz) δ: 1.23 (d, 2H), 1.32-1.45 (m, 4H), 1.72 (t, 2H), 1.81 (t, 2H), 1.93 (m, 2H), 2.16 (t, 2H), 2.60 (t, 2H), 3.15 (t, 2H), 6.77 (m, 2H), 7.08 (t, 1H). LRMS: ES ⁻ m/z 338 (M-H). CHN: 0.51 CH ₂ Cl ₂ |

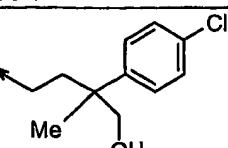
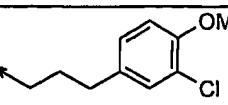
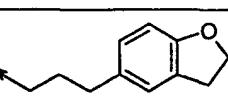
| Ex | Prec | R ¹ | -X-Y | Data |
|----|---------|------------------|------|---|
| 39 | Prep 39 | H | | ¹ HNMR (CD ₃ OD, 400MHz) δ: 1.45 (m, 2H), 1.51-1.65 (m, 4H), 1.75 (t, 2H), 1.80 (t, 2H), 1.95 (m, 2H), 2.15 (t, 2H), 2.61 (t, 2H), 3.18 (t, 2H), 6.85-7.95 (m, 3H). LRMS: ES ⁻ m/z 338 (M-H). CHN: 0.08 H ₂ O |
| 40 | Prep 40 | H | | ¹ HNMR (CD ₃ OD, 400MHz) δ: 1.47 (m, 2H), 1.52-1.69 (m, 4H), 1.75 (t, 2H), 1.88 (t, 2H), 2.0 (m, 2H), 2.17 (t, 2H), 2.60 (t, 2H), 3.18 (t, 2H), 7.1 (d, 2H), 7.23 (d, 2H), 7.68 (brs, 1H). LRMS: ES ⁻ m/z 386 (M-H). CHN: 0.1 H ₂ O |
| 41 | Prep 41 | (S)-methoxyethyl | | ¹ HNMR (CDCl ₃ , 300MHz) δ: 1.40-2.80 (m, 12H), 2.16-2.43 (m, 2H), 2.90-3.08 (m, 2H), 3.18-3.50 (m, 7H), 6.18 (s, 1H), 7.20-7.31 (m, 2H), 7.77 (t, 1H), 8.50 (d, 1H). |
| 42 | Prep 42 | H | | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.35-1.43 (m, 2H), 1.55-1.65 (m, 4H), 1.66-1.90 (m, 6H), 1.97-2.05 (m, 2H), 2.20-2.29 (m, 2H), 2.58 (t, 2H), 2.80-2.90 (m, 4H), 3.24-3.30 (m, 2H), 5.49 (bs, 1H), 6.90 (d, 1H), 6.92 (s, 1H), 7.10 (d, 1H). LRMS: ES ⁻ m/z 342 (M-H). Found: C, 73.71, 73.77; H, 9.08, 9.18; N, 3.36, 3.36. Requires: C, 73.81; H, 9.06; N, 3.75 (M + 0.06 EtOAc + 0.34 pentane) |
| 43 | Prep 43 | (S)-methoxyethyl | | ¹ HNMR (CDCl ₃ , 300MHz) δ: 1.50-2.12 (m, 14H), 2.48-2.62 (m, 3H), 3.23-3.47 (m, 7H), 4.25 (s, 3H), 5.77 (t, 1H), 6.65-6.75 (m, 2H), 6.81 (d, 2H). LRMS: TS ⁺ m/z 420 (M+H). |
| 44 | Prep 44 | (S)-methoxyethyl | | ¹ HNMR (CDCl ₃ , 300MHz) δ: 1.37-2.02 (m, 14H), 2.40-2.51 (m, 1H), 2.68-2.83 (q, 2H), 3.23-3.50 (m, 7H), 5.61 (s, 1H), 7.22-7.38 (m, 3H), 7.67-7.90 (m, 3H), 8.72 (d, 1H). LRMS: TS ⁺ m/z 439 (M+H). |

| Ex | Prec | R ¹ | -X-Y | Data |
|----|---------|----------------|---|--|
| 45 | Prep 45 | H |  | ¹ HNMR (CD ₃ OD, 400MHz) δ: 1.42-1.51 (m, 2H), 1.55-1.68 (m, 4H), 1.72-1.79 (m, 2H), 1.83-1.90 (m, 2H), 1.98-2.05 (m, 2H), 2.17 (t, 2H), 2.55 (t, 2H), 3.17 (t, 2H), 7.06 (d, 2H), 7.35 (d, 2H). LRMS: ES ⁻ m/z 380 (M-H). Found: C, 57.52, 57.59; H, 6.65, 6.66; N, 3.37, 3.35. Requires: C, 57.19; H, 6.58; N, 3.58 (M + 0.13 pentane) |
| 46 | Prep 46 | H |  | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.41-1.55 (m, 2H), 1.57-1.73 (m, 4H), 1.82-2.00 (m, 6H), 2.33 (t, 2H), 2.78 (t, 2H), 3.33 (q, 2H), 4.07 (s, 3H), 5.59 (t, 1H), 7.22-7.36 (m, 2H), 7.51 (s, 1H), 7.91 (s, 1H). |
| 47 | Prep 67 | H |  | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.45-1.52 (m, 2H), 1.58-1.65 (m, 4H), 1.75-1.90 (m, 4H), 1.93-1.95 (m, 2H), 2.25-2.29 (m, 2H), 2.66 (t, 2H), 3.22-3.30 (m, 2H), 5.67 (bs, 1H), 7.27 (d, 2H), 7.51 (d, 2H). ES ⁻ m/z 327 (M-H). Found: C, 58.78, 58.89; H, 6.96, 6.96; N, 6.40, 6.41. Requires: C, 58.57; H, 6.58; N, 6.80 (M + 1.17 water + 0.55 TFA). |
| 48 | Prep 47 | H |  | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.49 (m, 2H), 1.65 (m, 4H), 1.90 (m, 6H), 2.30 (t, 2H), 2.77 (t, 2H), 3.35 (q, 2H), 4.27 (s, 3H), 5.63 (brs, 1H), 7.23 (d, 2H), 7.45 (s, 1H), 7.70 (d, 2H), 7.87 (s, 1H). LRMS: m/z 358 (M+H), TS. |
| 49 | Prep 48 | H |  | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.40-1.53 (m, 2H), 1.74-2.03 (m, 12H), 2.28 (t, 2H), 2.56 (t, 2H), 2.77 (t, 2H), 3.27 (t, 2H), 4.14 (t, 2H), 5.56 (brs, 1H), 6.71 (d, 1H), 6.82 (s, 1H), 6.88 (d, 1H). LRMS: m/z 358 (M-H), ES ⁻ . Anal. Found C, 69.81; H, 8.09; N, 3.88%. C ₂₁ H ₂₉ NO ₄ requires C, 70.17; H, 8.13; N, 3.90%. |

| Ex | Prec | R ¹ | -X-Y | Data |
|----|---------|------------------|---|--|
| 50 | Prep 49 | H |  | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.37-1.45 (m, 2H), 1.56-1.59 (m, 4H), 1.73-1.90 (m, 6H), 2.23 (t, 2H), 2.40 (s, 3H), 2.55 (t, 2H), 3.24 (dt, 2H), 5.60 (brs, 1H), 7.05 (d, 2H), 7.14 (d, 2H). LRMS: m/z 348 (M-H), ES ⁺ . Anal. Found C, 63.68; H, 7.66; N, 3.67%. C ₁₉ H ₂₇ NO ₃ S.0.09 TFA requires C, 64.04; H, 7.59; N, 3.89%. |
| 51 | Prep 50 | H |  | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.20 (d, 3H), 1.40 (m, 2H), 1.50-1.90 (m, 10H), 2.20 (m, 2H), 2.60 (m, 1H), 3.05 (m, 1H), 3.15 (t, 2H), 3.25 (m, 1H), 4.50 (t, 2H), 5.50 (brs, 1H), 6.70 (d, 1H), 6.90 (d, 1H), 7.0 (s, 1H). LRMS: m/z 358 (M-H), ES ⁺ . |
| 52 | Prep 51 | H |  | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.10 (d, 3H), 1.40 (m, 2H), 1.60 (m, 6H), 1.90 (m, 4H), 2.30 (m, 2H), 2.50 (t, 2H), 3.10 (t, 2H), 4.00 (m, 1H), 4.50 (t, 2H), 5.40 (d, 1H), 6.65 (d, 1H), 6.85 (d, 1H), 6.95 (s, 1H). LRMS: m/z 358 (M-H), ES ⁺ . |
| 53 | Prep 52 | (S)-methoxyethyl |  | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.45-1.64 (m, 8H), 1.78-1.94 (m, 6H), 2.41 (s, 3H), 2.45-2.50 (m, 1H), 2.58 (t, 2H), 3.22-3.27 (m, 5H), 3.32-3.37 (m, 2H), 5.72 (brs, 1H), 7.07 (d, 2H), 7.15 (d, 2H). LRMS: m/z 406 (M-H), ES ⁺ . Anal. Found C, 65.02; H, 8.54; N, 2.87%. C ₂₂ H ₃₃ NO ₄ S.0.26 EtOAc requires C, 64.84; H, 8.46; N, 3.16%. |
| 54 | Prep 53 | H |  | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.43-1.53 (m, 3H), 1.58-1.69 (m, 8H), 1.70-1.82 (m, 1H), 1.83-2.01 (m, 4H), 2.28 (t, 2H), 3.33 (t, 2H), 3.42 (m, 1H), 4.23 (t, 1H), 4.60 (t, 1H), 5.70 (brs, 1H), 6.78 (dd, 1H), 6.88 (t, 1H), 7.11 (t, 1H), 7.18 (dd, 1H). LRMS: m/z 330 (M-H), ES ⁺ 332 MH ⁺ 354 MNa ⁺ ES ⁺ . Anal. Found C, 69.81; H, 8.09; N, 3.88%. C ₂₁ H ₂₉ NO ₄ requires C, 70.17; H, 8.13; N, 3.90%. |

| Ex | Prec | R ¹ | -X-Y | Data |
|----|---------|---------------------------|---|---|
| 55 | Prep 54 | (S)-methoxy ethyl |  | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.47-1.70 (m, 8H), 1.73-1.79 (m, 2H), 1.94-2.06 (m, 5H), 2.45-2.51 (m, 1H), 2.55 (t, 2H), 3.15-3.18 (m, 4H), 3.23 (s, 3H), 3.33-3.36 (m, 2H), 4.53 (t, 2H), 6.26 (brs, 1H), 6.75 (dd, 1H), 6.89 (d, 1H), 7.02 (d, 1H). LRMS: m/z 402 (M-H), ES ⁺ . Anal. Found C, 66.36; H, 8.20; N, 3.29%. C ₂₃ H ₃₃ NO ₅ .0.14 TFA requires C, 66.66; H, 7.96; N, 3.34%. |
| 56 | Prep 55 | (S)-methoxy ethyl |  | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.50-1.70 (m, 6H), 1.80 (t, 2H), 1.90-2.05 (m, 5H), 2.20 (s, 3H), 2.50 (m, 2H), 2.55 (t, 2H), 3.15 (t, 2H), 3.30 (m, 5H), 3.40 (m, 2H), 4.50 (t, 2H), 5.80 (brs, 1H), 6.70 (s, 1H), 6.85 (s, 1H). LRMS: m/z 432 (M-H), ES ⁺ . |
| 57 | Prep 56 | (S)-methoxy ethoxy methyl |  | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.43-2.06 (m, 12H), 2.57 (t, 2H), 2.63 (brm, 1H), 3.18 (t, 2H), 3.27 (q, 2H), 3.34 (s, 3H), 3.44-3.53 (m, 3H), 3.58 (t, 2H), 3.64 (brt, 1H), 4.53 (t, 2H), 5.90 (brs, 1H), 6.68 (d, 1H), 6.89 (d, 1H), 7.00 (s, 1H). LRMS: m/z 432 (M-H), ES ⁺ . Anal. Found C, 64.90; H, 8.16; N, 2.99%. C ₂₄ H ₃₅ NO ₆ .0.5H ₂ O requires C, 65.14; H, 8.20; N, 3.16%. |
| 58 | Prep 57 | (S)-methoxy ethoxy methyl |  | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.42 (s, 6H), 1.47-1.67 (m, 7H), 1.76-1.86 (m, 4H), 2.04 (dd, 1H), 2.55 (t, 2H), 2.59-2.65 (m, 1H), 2.94 (s, 2H), 3.23-3.28 (m, 2H), 3.32 (s, 3H), 3.46-3.50 (m, 3H), 3.55-3.62 (m, 3H), 6.00 (brs, 1H), 6.60 (d, 1H), 6.87 (d, 1H), 6.92 (s, 1H). LRMS: m/z 460 (M-H), ES ⁺ . Anal. Found C, 56.62; H, 6.93; N, 2.41%. C ₂₆ H ₃₉ NO ₆ .1.2 TFA requires C, 57.00; H, 6.77; N, 2.34%. |

| Ex | Prec | R ¹ | -X-Y | Data |
|----|---------|------------------------|------|--|
| 59 | Prep 58 | (R)-methyl | | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.08 (s, 3H), 1.42-1.76 (m, 7H), 1.80 (t, 2H), 1.88-2.0 (m, 2H), 2.10 (m, 1H), 2.45 (m, 1H), 2.60 (t, 2H), 3.28 (m, 2H), 5.80 (brs, 1H), 6.82-6.92 (m, 2H), 6.95 (dd, 1H). LRMS: m/z 396 (M-H) ES ⁻ 398 MH ⁺ 420 MNa ⁺ ES ⁺ . Anal. Found C, 55.84; H, 6.20; N, 3.01%. C ₂₀ H ₂₅ F ₂ NO ₅ .1H ₂ O.0.21CH ₂ Cl ₂ requires C, 56.03; H, 6.38; N, 3.23%. |
| 60 | Prep 59 | (S)-methoxyethyl | | ¹ HNMR (CDCl ₃ , 300MHz) δ: 1.20 (d, 3H), 1.40-1.85 (m, 12H), 1.95 (m, 2H), 2.45 (m, 1H), 2.65 (m, 1H), 3.05 (m, 1H), 3.15 (t, 2H), 3.25 (s, 3H), 3.30 (m, 3H), 4.50 (t, 2H), 5.60 (brs, 1H), 6.70 (d, 1H), 6.90 (d, 1H), 7.00 (s, 1H). LRMS: m/z 416 (M-H), ES ⁻ . |
| 61 | Prep 60 | (S)-methoxyethyl | | ¹ HNMR (CDCl ₃ , 300MHz) δ: 1.50-1.70 (m, 8H), 1.75 (t, 2H), 1.90-2.10 (m, 4H), 2.21 (s, 3H), 2.50 (m, 1H), 2.60 (t, 2H), 3.25 (s, 3H), 3.30 (m, 2H), 3.35 (m, 2H), 4.50 (m, 2H), 5.80 (brs, 1H), 6.60 (s, 1H), 6.95 (s, 1H). LRMS: m/z 416 (M-H), ES ⁻ . |
| 62 | Prep 61 | (S)-methoxyethoxyethyl | | ¹ HNMR (CDCl ₃ , 300MHz) δ: 1.50 (m, 2H), 1.60-2.00 (m, 10H), 2.60 (m, 3H), 3.20 (t, 2H), 3.30 (s, 3H), 3.45 (m, 3H), 3.55 (m, 2H), 3.60 (m, 1H), 6.0 (brs, 1H), 7.02 (d, 2H), 7.19 (d, 2H). LRMS: m/z 424 (M-H), ES ⁻ . |
| 63 | Prep 62 | (S)-methoxyethyl | | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.3 (s, 6H), 1.4-1.79 (m, 10H), 1.8 (t, 2H), 1.93 (m, 2H), 2.42 (m, 1H), 3.17 (m, 4H), 3.3 (s, 3H), 3.38 (m, 2H), 4.55 (t, 2H), 5.5 (brs, 1H), 6.7 (d, 1H), 7.1 (d, 1H), 7.2 (s, 1H). LRMS: M-H, 430. (ES ⁻) |
| 64 | Prep 63 | (S)-methoxyethyl | | ¹ HNMR (CDCl ₃ , 300MHz) δ: 1.40-2.23 (m, 15H), 2.43-2.63 (m, 1H), 2.80-2.95 (m, 1H), 3.29 (s, 3H), 3.03-3.57 (m, 3H), 3.60-3.83 (m, 2H), 5.99 (br.s, 1H), 7.19 (d, 2H), 7.30 (d, 2H). LRMS: M+H, 426. (TS ⁺) |

| Ex | Prec | R ¹ | -X-Y | Data |
|----|---------|-------------------|---|---|
| 65 | Prep 64 | (S)-methoxy ethyl |  | ¹ H NMR (CDCl ₃ , 300MHz) δ: 1.17-2.17 (m, 17H), 2.40-2.58 (m, 1H), 2.98-3.57 (m, 7H), 3.61-3.77 (m, 2H), 5.93 (br.s, 1H), 7.20-7.43 (m, 4H). LRMS: M+H, 440. (TS ⁺) |
| 66 | Prep 65 | (S)-methoxy ethyl |  | ¹ H NMR (CDCl ₃ , 300MHz) δ: 1.40-2.18 (m, 16H), 2.43-2.68 (m, 3H), 3.30 (s, 3H), 3.26-3.48 (m, 2H), 3.88 (s, 3H), 5.83 (brs, 1H), 6.83 (d, 1H), 7.04 (d, 1H), 7.20 (s, 1H). Anal. Found C, 60.01; H, 7.60; N, 3.00%. C ₂₂ H ₃₂ ClNO ₅ ·0.75H ₂ O requires C, 60.13; H, 7.68; N, 3.19%. |
| 67 | Prep 66 | (S)-methoxy ethyl |  | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.42 (d, 3H), 1.45-1.66 (8H), 1.74-1.80 (m, 2H), 1.82-1.95 (m, 3H), 1.97-2.02 (1H), 2.42-2.55 (m, 3H), 2.75 (dd, 1H), 3.20-3.27 (m, 6H), 3.31-3.36 (m, 2H), 4.80-4.87 (m, 1H), 5.77 (brs, 1H), 6.61 (d, 1H), 6.85 (d, 1H), 6.93 (s, 1H). LRMS: M+Na, 440. (ES ⁺) |

Alternatively Example 22 may be prepared as follows:

(2S)-2-[(1-({[3-(4-Chlorophenyl)propyl]amino} carbonyl)cyclopentyl)methyl]-4-methoxybutanoic acid

- 5 To a solution of the product from Preparation 22 (9.6 g, 21.2 mmol) in dichloromethane (52 ml) was added trifluoroacetic acid (16.3 ml, 212 mmol) and the resultant solution was stirred at room temperature for 3.75 hours under an atmosphere of N₂. To the reaction was then added aqueous sodium carbonate solution (95 ml of a 10% w/v solution) with stirring until the pH of the aqueous layer was between pH 2 and 3. The layers were then separated and the organic layer was extracted with aqueous sodium carbonate solution (2 x 20 ml of a 10% w/v solution). The aqueous layers were combined and saturated brine (80 ml) was then added, followed by 2-butanone (40 ml). The layers were separated and the aqueous layer was extracted again with 2-butanone (2 x 50 ml). The combined organic layers were then dried by azeotropic distillation at atmospheric pressure to a volume of 70 ml whereupon crystallisation occurred and the mixture was diluted with 2-butanone (70 ml). The product was then collected by filtration and dried at 50 °C for 65 hours under vacuum to give the crude sodium salt of the title compound as a white solid (5.76 g) that was then purified by recrystallisation as follows. To the crude product was added ethyl acetate (87 ml) and ethanol (13 ml) and the remaining insoluble material was removed by filtration. The ethanol was then removed by azeotropic
- 10
- 15
- 20

distillation at atmospheric pressure (to remove 110 ml of solvent) and replaced with ethyl acetate (145 ml) whereupon crystallisation occurred. The resultant crystallised product was then collected by filtration under vacuum to give the pure sodium salt of the title product as a white crystalline solid (4.51 g, 10.8 mmol, 51 %); m.p. (ethyl acetate) 214-5 216 °C; ¹H NMR (DMSO-d₆ 300MHz) δ: 1.26-1.58 (m, 8 H), 1.62-1.74 (m, 3 H), 1.74-1.86 (m, 1 H), 1.91-2.07 (m, 3 H), 2.57 (t, 2 H), 3.03 (q, 2 H), 3.10 (s, 3 H), 3.13-3.27 (m, 2 H), 7.22 (d, 2 H), 7.29 (d, 2 H), 9.16 (t, br, 1 H); LRMS (ES negative); 789 [2M-H]⁻ (³⁵Cl), 394 [M-H]⁻ (³⁵Cl). For analytical purposes the title product (i.e. the free acid) was obtained by dissolving this sodium salt in water, acidified with 5 M hydrochloric acid and 10 extracted with dichloromethane. Removal of the solvent by blowing a stream of nitrogen over the sample gave the title product; ¹H NMR (DMSO-d₆ 300MHz) δ: 1.22-1.80 (m, 11 H), 1.81-1.96 (m, 2 H), 1.96-2.08 (m, 1 H), 2.93-2.27 (m, 1 H), 2.53 (t, 2 H), 3.03 (q, 2 H), 3.11 (s, 3 H), 3.16-3.25 (m, 2 H), 7.20 (d, 2 H), 7.30 (d, 2 H), 7.51 (t, 1 H); LRMS (ES negative); 789 [2M-H]⁻ (³⁵Cl), 394 [M-H]⁻ (³⁵Cl); HPLC (column: ChiralPak AS (25 x 0.46 15 cm); mobile phase: hexane/IPA/acetic acid (95/5/0.5 v/v/v); flow rate: 1.0 ml/min; temperature: ambient; injection volume: 20 μl; detection: UV@ 220 nm; Sample concentration: 1.0 mg/ml prepared in mobile phase) Retention Time: minor enantiomer 11.4 min (5.7%), major enantiomer 14.3 min (94.3%).

20 Sodium Salts of Example 22

a) Mono-hydrate

To the sodium salt of Example 22 (200 mg) was added to 1 ml of a 3.9% water in isopropanol solution. The resulting slurry was stirred for 12 days whereupon it was isolated by filtration. The product gave the following PXRD pattern.

25

| Angle 2-Theta ° | Intensity % |
|--------------------|----------------|--------------------|----------------|--------------------|----------------|--------------------|----------------|
| 3.552 | 30.8 | 17.708 | 13.5 | 22.881 | 35 | 30.672 | 15 |
| 7.154 | 8 | 17.93 | 29 | 23.141 | 23.2 | 30.952 | 17.5 |
| 9.526 | 3.1 | 18.313 | 12 | 23.478 | 15.1 | 31.437 | 15.7 |
| 10.359 | 15.7 | 18.545 | 23.9 | 24.088 | 13.9 | 31.788 | 13.9 |
| 10.608 | 14.3 | 18.811 | 14 | 24.313 | 12.6 | 32.114 | 24.6 |
| 11.03 | 5 | 19.7 | 34.2 | 24.588 | 22.7 | 32.998 | 13.3 |
| 12.369 | 3.7 | 19.978 | 100 | 25.013 | 25.8 | 33.375 | 18.8 |
| 12.939 | 13.2 | 20.273 | 90.6 | 25.514 | 29.9 | 33.815 | 14 |
| 13.233 | 12.3 | 20.627 | 51.9 | 25.987 | 25.5 | 34.266 | 14.4 |
| 13.835 | 14.2 | 20.829 | 29.4 | 27.107 | 18.2 | 35.705 | 15.7 |
| 14.345 | 37.9 | 20.926 | 28.4 | 27.395 | 30.6 | 35.989 | 14.1 |
| 14.887 | 16 | 21.443 | 52.7 | 27.869 | 19.2 | 36.514 | 16.7 |
| 15.16 | 16.8 | 21.611 | 41.6 | 28.716 | 21 | 38.151 | 14.6 |

| | | | | | | | |
|--------|------|--------|------|--------|------|--------|----|
| 16.372 | 24.9 | 21.881 | 21.2 | 28.788 | 19 | 38.925 | 17 |
| 16.813 | 6.9 | 22.174 | 24.3 | 28.989 | 27.2 | 39.091 | 19 |
| 17.203 | 22.1 | 22.472 | 47.1 | 30.232 | 13.4 | 39.961 | 13 |
| 17.408 | 32.7 | | | | | | |

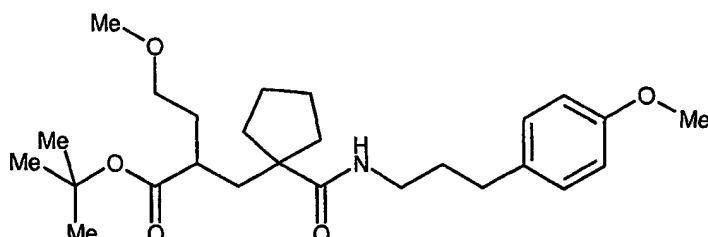
Differential scanning calorimetry (DSC) was performed using a Perkin Elmer DSC-7 instrument fitted with an automatic sample changer. Approximately 3mg of the sample was accurately weighed into a 50 microlitre aluminium pan and crimp sealed with a

5 perforated lid. The samples were heated at 20°C/minute over the range 40°C to 300°C with a nitrogen gas purge. Dehydration events occurred at between 50 and 150 °C and a main melt between 212 and 225 °C. The skilled person will appreciate that the melting point may vary outside this range as a result of sample impurity.

10 b) Anhydrous salt

The sodium salt of Example 22 gave the following PXRD pattern.

| Angle 2-Theta ° | Intensity % |
|--------------------|----------------|--------------------|----------------|--------------------|----------------|--------------------|----------------|
| 5.463 | 12.2 | 17.714 | 95.6 | 22.735 | 30 | 28.926 | 23.8 |
| 6.654 | 100 | 18.083 | 31.7 | 23.36 | 56.5 | 29.802 | 23.5 |
| 7.546 | 66 | 18.64 | 28.8 | 24.126 | 31.9 | 30.454 | 30.7 |
| 9.336 | 31.3 | 18.902 | 82.4 | 24.388 | 45.2 | 30.885 | 29.2 |
| 10.953 | 9.7 | 19.696 | 40.1 | 24.72 | 25.8 | 31.48 | 21 |
| 11.571 | 55.9 | 20.406 | 33.9 | 25.298 | 26.7 | 32.66 | 16.8 |
| 12.56 | 10.9 | 20.502 | 31.8 | 25.579 | 20.4 | 34.027 | 23.1 |
| 13.287 | 22.9 | 20.683 | 45.4 | 26.718 | 17.6 | 34.494 | 17.6 |
| 15.125 | 33.6 | 20.942 | 31.5 | 27.151 | 24.2 | 36.011 | 19 |
| 15.667 | 60.3 | 21.559 | 92.6 | 27.46 | 22.7 | 36.997 | 17.4 |
| 16.403 | 17.2 | 21.898 | 66.2 | 27.737 | 20.2 | 38.704 | 21.2 |
| 17.024 | 62.2 | 22.274 | 36.6 | 28.56 | 27.1 | 39.961 | 18.7 |

PREPARATIONSPREPARATION 1tert-Butyl 4-methoxy-2-[(1-((3-(4-methoxyphenyl)propyl)amino)carbonyl)-cyclopentyl]methyl]butanoate

The product from Preparation 68 (325mg, 1.08mmol), the product of Preparation 73 (178mg, 1.08mmol), HOBr (146mg, 1.08mmol), WSCDI (207mg, 1.08mmol) and triethylamine (0.3ml, 2.16mmol) were stirred together in dichloromethane (5ml) at room temperature for 14 hours. The reaction mixture was diluted with dichloromethane (10ml) and washed with water (2x20ml). The organic layer was dried over magnesium sulphate, filtered and concentrated *in vacuo*. The product was purified by column chromatography using dichloromethane, then 99:1 dichloromethane:methanol, then 98:2 dichloromethane:methanol (R_f 0.2) to give the product as a yellow oil (267mg, 0.6mmol); ^1H NMR (CDCl_3 400MHz) δ : 1.4 (s, 9H), 1.6 (m, 5H), 1.8 (m, 4H), 2.0 (m, 1H), 2.3 (m, 1H), 2.6 (t, 2H), 3.2 (s, 3H), 3.3 (m, 2H), 3.7 (s, 3H), 5.7 (t, 1H), 6.8 (d, 2H), 7.0 (d, 2H); LRMS: m/z 448 (M-H $^+$).

The following Examples of formula (IVa), i.e. compounds of general formula IV where prot is *tert*-butyl, were prepared by methods similar to Preparation 1, from the precursors indicated (see Table 2).

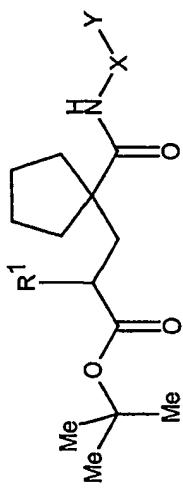
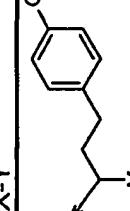
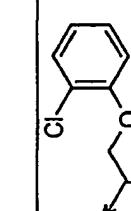
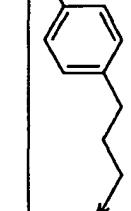
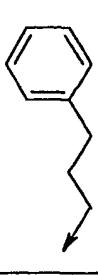
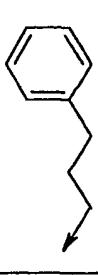
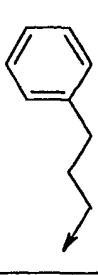
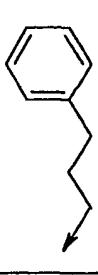
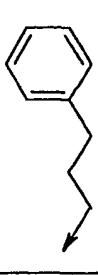
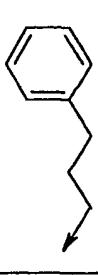
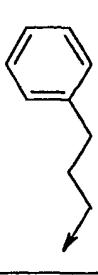
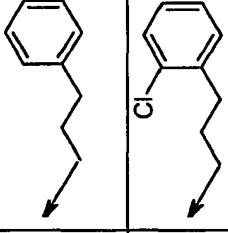
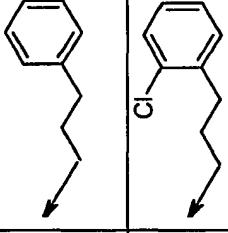
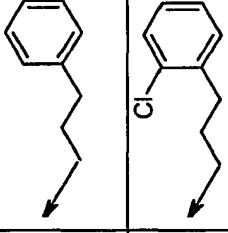
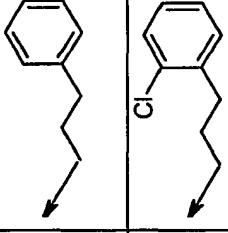
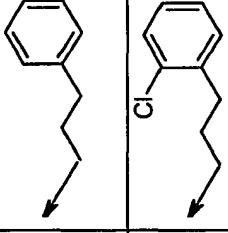
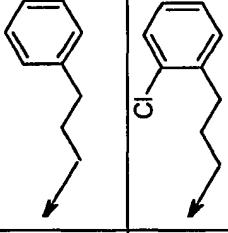
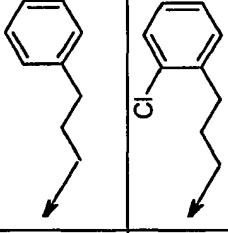


Table 2

| Prep | Prec. acid | Prec. amine | R¹ | -X-Y | Analytical Data |
|------|------------|---|--------------|--|--|
| 2 | Prep 68 | Commercially available from ICN Biomedicals Inc | methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4 (s, 9H), 1.6-2.0 (m, 16H), 2.3 (m, 1H), 2.6 (t, 2H), 3.2 (d, 3H), 3.3 (m, 3H), 3.7 (s, 3H), 4.0 (m, 1H), 5.5 (bs, 1H), 6.8 (d, 2H), 7.1 (d, 2H). LRMS: m/z 462 (M-H ⁺). |
| 3 | Prep 68 | Prep 120 | methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4-1.45 (m, 10H), 1.5-1.7 (m, 6H), 1.7-1.8 (m, 2H), 1.9-2.1 (m, 4H), 2.3-2.4 (m, 1H), 3.1 (d, 3H), 3.1-3.35 (m, 3H), 3.9-4.0 (m, 2H), 4.3-4.4 (m, 1H), 6.1-6.2 (m, 1H), 6.8-6.9 (s, 2H), 7.2 (t, 1H), 7.3 (d, 1H). |
| 4 | Prep 68 | US 4533655, Example 7A | methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4 (s, 9H), 1.5 (m, 2H), 1.6 (m, 4H), 1.7 (dd, 3H), 1.8 (m, 2H), 1.9 (m, 3H), 2.3 (m, 1H), 2.6 (t, 2H), 3.1 (m, 1H), 3.2 (s, 3H), 3.3 (t, 2H), 5.9 (m, 1H), 6.9 (t, 2H), 7.1 (t, 2H). LRMS: m/z 436 (M-H ⁺). |

| Prep | Prec. acid | Prec. amine | R ¹ | -X-Y | Analytical Data |
|------|------------|--|----------------|--|--|
| 5 | Prep 68 | Commercially available from Aldrich Chemical Company | methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4 (s, 9H), 1.5-1.6 (m, 10H), 1.7 (m, 2H), 2.0 (m, 4H), 2.3 (m, 1H), 2.6 (t, 2H), 3.2 (s, 5H), 3.3 (t, 2H), 5.9 (bs, 1H), 7.1 (m, 3H), 7.2 (t, 2H), 10.4 (bs, 1H). LRMS: m/z 432 (M-H ⁺). |
| 6 | Prep 68 | Commercially available from Aldrich Chemical Company | methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4 (s, 9H), 1.45 (m, 2H), 1.6 (m, 8H), 1.8 (m, 4H), 2.3 (m, 1H), 2.6 (t, 2H), 3.2 (s, 3H), 3.3 (m, 4H), 3.8 (bs, 1H), 7.1 (d, 3H), 7.2 (d, 2H). LRMS: m/z 418 (M-H ⁺). |
| 7 | Prep 68 | Bioorg. Med. Chem., 1997, 5, 1675-83 | methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4 (s, 10H), 1.6 (m, 10H), 1.8 (m, 2H), 2.3 (m, 1H), 2.6 (t, 2H), 3.2 (s, 3H), 3.3 (m, 4H), 5.7 (bs, 1H), 6.7 (d, 2H), 7.0 (d, 2H). LRMS: m/z 434 (M-H ⁺). |
| 8 | Prep 68 | Bioorg. Med. Chem., 1997, 5, 1675-83 | methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.5 (s, 9H), 1.6 (m, 15H), 2.7 (m, 2H), 3.25 (s, 2H), 3.3 (m, 4H), 5.9 (s, 1H), 7.3 (m, 2H), 7.3 (m, 2H). LRMS: m/z 486 (M-H ⁺). |
| 9 | Prep 68 | Prep 74 | methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.2 (t, 3H), 1.4 (s, 11H), 1.6 (m, 9H), 1.8 (m, 3H), 1.9 (m, 2H), 2.3 (q, 1H), 2.6 (q, 4H), 3.2 (s, 3H), 3.3 (m, 2H), 3.35 (t, 2H), 5.8 (bs, 1H), 7.1 (s, 4H). LRMS: m/z 446 (M-H ⁺). |
| 10 | Prep 68 | Prep 75 | methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4 (s, 9H), 1.45 (m, 2H), 1.5-2.03 (m, 12H), 2.28 (s, 3H), 2.38 (m, 1H), 2.59 (t, 2H), 3.25 (s, 3H), 3.33 (m, 4H), 3.78 (s, 3H), 5.79 (s, 1H), 6.7 (m, 2H), 7.03 (d, 1H). LRMS: m/z 462 (M+H ⁺). |
| 11 | Prep 68 | Prep 76 | methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.40 (s, 9H), 1.6 (m, 10H), 1.8 (m, 3H), 1.9 (m, 2H), 2.3 (m, 1H), 2.6 (t, 2H), 3.1 (t, 2H), 3.2 (s, 3H), 3.3 (q, 2H), 4.5 (t, 2H), 5.7 (m, 1H), 6.9 (d, 1H), 7.0 (s, 1H). LRMS: m/z 460 (M-H ⁺). |

| Prep | Prec. acid | Prec. amine | R ¹ | -X-Y | Analytical Data |
|------|------------------------|---|----------------|--|---|
| 12 | Prep 68 | Commercially available from Xenobiotica | methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4 (s, 10H), 1.5-1.7 (m, 6H), 1.7-1.85 (m, 4H), 1.9-2.0 (m, 3H), 2.3-2.4 (m, 1H), 2.6-2.7 (m, 2H), 3.2 (d, 2H), 3.3 (s, 3H), 3.3-3.4 (m, 2H), 6.3 (bs, 1H), 6.9 (t, 2H), 7.0.5 (dd, 2H). LRMS: m/z 434 (M+H ⁺). |
| 13 | Prep 68 | J. Med. Chem., 1996, 39(20), 4017 | methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4 (s, 10H), 1.5-2.0 (m, 14H), 2.3-2.4 (m, 1H), 2.6 (t, 2H), 3.2 (s, 3H), 3.2-3.3 (m, 3H), 3.4-3.5 (m, 2H), 5.8 (bs, 1H), 7.0 (d, 1H), 7.1-7.2 (m, 3H). LRMS: m/z 452 (M+H ⁺). |
| 14 | Prep 68 | Tet. Lett., 1999, 40, 2033-4 | methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4-1.45 (m, 10H), 1.5-2.0 (m, 13H), 2.3-2.4 (m, 1H), 2.7 (t, 2H), 3.2 (s, 3H), 3.25-3.35 (m, 4H), 5.8 (bs, 1H), 7.05-7.3 (m, 4H). LRMS: m/z 452 (M+H ⁺). |
| 15 | Prep 68 | J. Med. Chem., 1996, 39, 4942-51 | methoxyethyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4 (s, 10H), 1.5-2.05 (m, 13H), 2.3-2.4 (m, 1H), 2.6 (t, 2H), 3.25 (s, 3H), 3.20-3.35 (m, 4H), 5.8 (bs, 1H), 7.1 (d, 2H), 7.2 (d, 2H). LRMS: m/z 452 (M+H ⁺). |
| 16 | Prep 71 | Prep 73 | (R)-propyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 0.8 (t, 3H), 1.2 (m, 6H), 1.4 (s, 9H), 1.4-1.9 (m, 10H), 2.2 (m, 1H), 2.5 (t, 2H), 3.2 (m, 2H), 3.7 (s, 3H), 5.6 (s, 1H), 6.8 (d, 2H), 7.1 (d, 2H). LRMS: m/z 432 (M-H). |
| 17 | Prep 70 | Prep 73 | (R)-methyl |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.11 (t, 3H), 1.38-2.10 (m, 21H), 2.03 (m, 2H), 2.33 (m, 1H), 2.62 (t, 2H), 3.28 (m, 2H), 3.80 (s, 3H), 5.73 (m, 1H), 6.83 (d, 2H), 7.12 (d, 2H). |
| 18 | EP274234B1, Example 35 | Prep 73 | H |  | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.43 (m, 9H), 1.48 (m, 2H), 1.65 (m, 4H), 1.83 (m, 4H), 1.99 (m, 2H), 2.19 (m, 2H), 2.61 (t, 2H), 3.29 (q, 2H), 3.8 (s, 3H), 5.59 (m, 1H), 6.84 (d, 2H), 7.11 (d, 2H). |

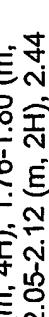
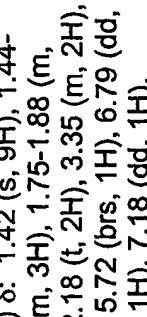
| Prep | Prec. acid | Prec. amine | R ¹ | -X-Y | Analytical Data |
|------|---------------------------|---|----------------------|------|---|
| 19 | EP274234B1, Example 35 | J. Med. Chem., 1996, 39(20), 4017 | H | | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.36-1.50 (m, 1H), 1.62 (m, 4H), 1.80 (m, 4H), 1.94 (m, 2H), 2.13 (m, 2H), 2.59 (t, 2H), 3.25 (q, 2H), 5.61 (m, 1H), 7.03 (d, 1H), 7.15 (m, 3H). |
| 20 | EP274234B1, Example 35 | J. Med. Chem., 1996, 39, 4942- 51 | H | | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.61-1.78 (m, 1H), 1.66 (m, 4H), 1.85 (m, 4H), 2.00 (m, 2H), 2.20 (m, 2H), 2.63 (t, 2H), 3.29 (q, 2H), 5.64 (m, 1H), 7.13 (d, 2H), 7.26 (d, 2H). |
| 21 | EP274234B1, Example 35 | Prep 76 | H | | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.35-1.45 (m, 1H), 1.61 (m, 4H), 1.78 (m, 4H), 1.92 (m, 2H), 2.14 (t, 2H), 2.53 (t, 2H), 3.14 (t, 2H), 3.24 (q, 2H), 4.50 (t, 2H), 5.53 (m, 1H), 6.66 (d, 1H), 6.84 (d, 1H), 6.98 (s, 1H). |
| 22 | Prep 69 | J. Med. Chem., 1996, 39, 4942- 51 | (S)- methoxyethyl | | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4 (s, 10H), 1.5-2.05 (m, 13H), 2.3-2.4 (m, 1H), 2.6 (t, 2H), 3.25 (s, 3H), 3.20-3.35 (m, 4H), 5.8 (bs, 1H), 7.1 (d, 2H), 7.2 (d, 2H). LRMS: m/z 452 (M-H). [α] _D +0.0 (MeOH, c 0.35). Anal. Found C, 65.95; H, 8.66; N, 3.25. C ₂₅ H ₃₈ NO ₄ ClO ₁ 18H ₂ O requires C, 65.95; H, 8.49; N, 3.08%. |
| 23 | Prep 69 | US 4533655, Example 7A | (S)- methoxyethyl | | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4 (s, 9H), 1.5-2.0 (m, 14H), 2.2 (m, 1H), 2.5 (m, 2H), 3.2 (s, 3H), 3.2-3.3 (m, 4H), 5.8 (bs, 1H), 6.9 (m, 2H), 7.1 (m, 2H). LRMS: m/z 436 (M-H ⁺). |
| 24 | Prep 69 | Prep 73 | (S)- methoxyethyl | | ¹ H NMR (CDCl ₃ 400MHz) δ: 1.4 (s, 9H), 1.5-2.0 (m, 15H), 2.3 (m, 1H), 2.6 (t, 2H), 3.2 (s, 3H), 3.2-3.3 (m, 3H), 3.3 (t, 2H), 3.7 (s, 3H), 5.7 (bs, 1H), 6.8 (d, 2H), 7.0 (d, 2H). LRMS: m/z 448 (M-H ⁺). HRMS m/z 448.3048 (C ₂₆ H ₄₁ NO ₅ requires 448.3058) |

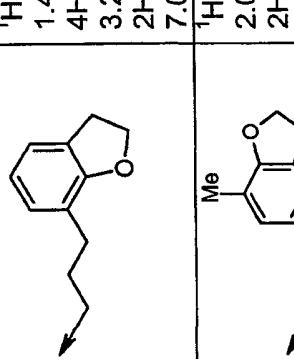
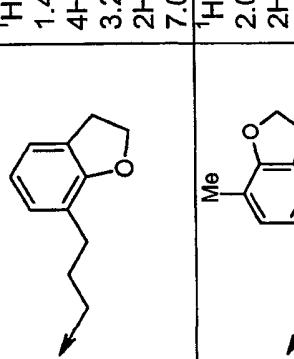
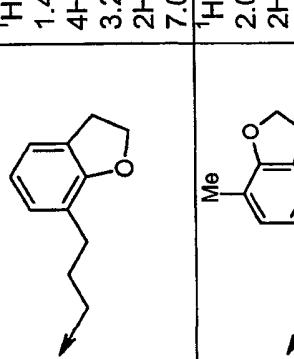
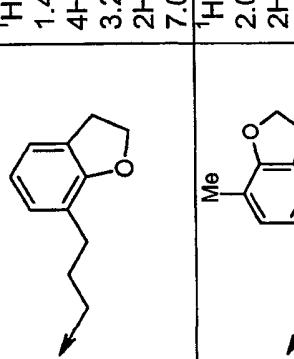
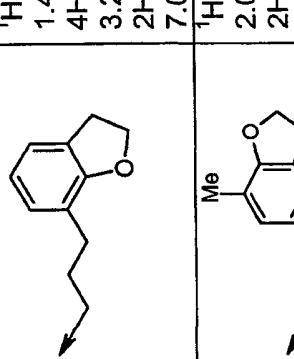
| Prep | Prec. acid | Prec. amine | R ¹ | -X-Y | Analytical Data |
|------|------------------------|-------------|------------------|------|---|
| 25 | Prep 69 | Prep 76 | (S)-methoxyethyl | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.40 (s, 9H), 1.50-2.03 (m, 16H), 2.30-2.39 (m, 1H), 2.57 (t, 2H), 3.16 (t, 2H), 3.24 (s, 3H), 3.32 (t, 2H), 4.55 (t, 2H), 5.78 (bs, 1H), 6.68 (d, 1H), 6.90 (d, 1H), 7.0 (s, 1H). LRMS: m/z 460 (M+H). HRMS m/z 460.3064 (C ₂₇ H ₄₂ NO ₅ requires 460.3057). |
| 26 | EP274234B1, Example 35 | Prep 99 | H | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.41 (s, 9H), 1.23-1.78 (m, 5H), 1.80-2.03 (m, 4H), 2.07-2.28 (m, 4H), 2.83 (dt, 2H), 3.00 (brs, 2H), 3.33 (q, 1H), 5.63 (brs, 1H), 7.37 (dd, 1H), 7.52-7.60 (m, 2H), 8.03 (dd, 2H), 8.84 (d, 1H). LRMS: ES ⁺ m/z 411 (M+H). |
| 27 | Prep 68 | Prep 82 | methoxyethyl | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.40 (s, 10H), 1.60 (m, 6H), 1.80 (m, 2H), 2.01 (m, 4H), 2.45 (m, 1H), 2.6 (t, 2H), 3.21 (m, 2H), 3.25 (s, 3H), 3.30 (s, 3H), 3.41 (m, 2H), 5.86 (brs, 1H), 6.90 (brm, 2H), 7.10 (m, 2H). LRMS: ES ⁺ m/z 448.8 (M+H). |
| 28 | Prep 68 | Prep 83 | methoxyethyl | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.40 (s, 9H), 1.60 (m, 4H), 1.80 (m, 4H), 2.10 (m, 4H), 2.31 (s, 3H), 2.42 (m, 1H), 2.60 (t, 2H), 3.21 (s, 3H), 3.40 (m, 4H), 5.81 (brs, 1H), 7.10 (s, 4H). |
| 29 | Prep 68 | Prep 84 | methoxyethyl | | ¹ H NMR (CDCl ₃ , 400 MHz) δ: 1.61 (m, 10H), 1.90 (m, 4H), 2.01 (m, 2H), 2.53 (m, 1H), 2.60 (t, 3H), 3.20 (m, 5H), 3.30 (q, 2H), 5.01 (s, 2H), 5.80 (brs, 1H), 6.90 (m, 3H), 7.21 (t, 1H), 7.40 (m, 5H). LRMS: ES ⁺ m/z 468 (M+H). |
| 30 | Prep 68 | Prep 85 | methoxyethyl | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.40 (m, 10H), 1.60 (m, 6H), 1.80 (m, 4H), 2.01 (m, 2H), 2.30 (m, 2H), 2.59 (t, 2H), 3.21 (s, 3H), 3.30 (m, 2H), 3.80 (d, 3H), 5.91 (brs, 1H), 6.21-6.39 (dd, 1H), 6.72 (dd, 1H), 6.90 (d, 1H), 7.11 (q, 1H). LRMS: ES ⁺ m/z 448 (M+H). |

| Prep | Prec. acid | Prec. amine | R ¹ | -X-Y | Analytical Data |
|------|------------------------|-------------|------------------|------|---|
| 31 | Prep 68 | Prep 86 | methoxyethyl | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.39 (s, 10H), 1.55-1.61 (m, 4H), 1.63-1.81 (m, 6H), 1.95 (m, 2H), 2.05 (dd, 2H), 2.55 (t, 2H), 3.20 (q, 2H), 3.22 (s, 3H), 3.30 (t, 2H), 3.78 (d, 6H), 5.88 (brt, 1H), 6.40 (m, 2H), 6.95 (d, 1H). LRMS: ES ⁺ m/z 478 (M+H). ¹ H NMR (CDCl ₃ , 300MHz) δ: 1.39-2.08 (25H, m), 2.34 (1H, m), 2.57 (2H, t), 3.20-3.28 (5H, m), 3.33 (2H, t), 3.78 (3H, s), 5.74 (1H, m), 6.81 (2H, d), 7.07 (2H, d). |
| 32 | Prep 69 | Prep 107 | (S)-methoxyethyl | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.20 (s, 9H), 1.60 (m, 4H), 1.75 (m, 2H), 1.80-2.00 (m, 6H), 2.10 (m, 2H), 3.05 (t, 2H), 3.30 (m, 2H), 5.60 (brs, 1H), 7.25 (m, 1H), 7.35 (m, 1H), 7.45 (m, 2H), 7.65 (d, 1H), 7.80 (d, 1H), 7.95 (d, 1H). LRMS: ES ⁺ m/z 410.2 (M+H). ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.40 (s, 9H), 4.42 (m, 2H), 1.60 (m, 4H), 1.80 (m, 2H), 1.90 (m, 4H), 2.10 (m, 2H), 2.80 (t, 2H), 3.30 (q, 2H), 5.60 (brs, 1H), 7.30 (d, 1H), 7.40 (m, 2H), 7.60 (s, 1H), 7.75 (m, 3H). LRMS: ES ⁺ m/z 410.2 (M+H). |
| 33 | EP274234B1, Example 35 | Prep 79 | H | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.4 (s, 9H), 4.42 (m, 2H), 1.60 (m, 4H), 1.80 (m, 2H), 1.90 (m, 4H), 2.10 (m, 2H), 2.80 (t, 2H), 3.30 (q, 2H), 5.60 (brs, 1H), 7.30 (d, 1H), 7.40 (m, 2H), 7.60 (s, 1H), 7.75 (m, 3H). LRMS: ES ⁺ m/z 410.2 (M+H). |
| 34 | EP274234B1, Example 35 | Prep 78 | H | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.4 (s, 9H), 4.42 (m, 2H), 1.60 (m, 4H), 1.80 (m, 2H), 1.90 (m, 4H), 2.10 (m, 2H), 2.80 (t, 2H), 3.30 (q, 2H), 5.60 (brs, 1H), 7.30 (d, 1H), 7.40 (m, 2H), 7.60 (s, 1H), 7.75 (m, 3H). LRMS: ES ⁺ m/z 410.2 (M+H). |
| 35 | Prep 69 | Prep 95 | (S)-methoxyethyl | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.4 (s, 9H), 1.55-1.81 (m, 13H), 1.8-2.0 (m, 3H), 2.35 (m, 1H), 2.55 (t, 2H), 3.21 (s, 3H), 3.22 (t, 2H), 3.30 (t, 2H), 5.82 (brs, 1H), 7.0 (dd, 2H), 7.18 (d, 1H). LRMS: ES ⁺ m/z 471 (M+H). ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.41 (s, 9H), 1.55-2.06 (m, 13H), 2.15-2.21 (m, 1H), 2.32-2.38 (m, 1H), 3.22 (s, 3H), 3.25-3.35 (m, 4H), 5.81 (brs, 1H), 6.90 (d, 1H), 6.95 (d, 1H), 7.22-7.24 (m, 1H). LRMS: TSP ⁺ m/z 470 (M+H). |
| 36 | Prep 69 | Prep 94 | (S)-methoxyethyl | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.41 (s, 9H), 1.55-2.06 (m, 13H), 2.15-2.21 (m, 1H), 2.32-2.38 (m, 1H), 3.22 (s, 3H), 3.25-3.35 (m, 4H), 5.81 (brs, 1H), 6.90 (d, 1H), 6.95 (d, 1H), 7.22-7.24 (m, 1H). LRMS: TSP ⁺ m/z 470 (M+H). |

| Prep | Prec. acid | Prec. amine | R' | -X-Y | Analytical Data |
|------|------------------------|-------------|------------------|------|---|
| 37 | Prep 69 | Prep 77 | (S)-methoxyethyl | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.4 (s, 9H), 1.55-1.80 (m, 11H), 1.85-2.05 (m, 3H), 2.36 (m, 1H), 2.60 (t, 2H), 3.21 (s, 3H), 3.25 (t, 2H), 3.30 (t, 2H), 5.85 (brs, 1H), 6.75 (q, 2H), 7.10 (q, 1H). LRMS: ES ⁺ m/z 454 (M+H). |
| 38 | EP274234B1, Example 35 | Prep 97 | H | | ¹ H NMR (CDCl ₃ , 300MHz) δ: 1.41 (s, 9H), 1.50 (m, 2H), 1.67 (m, 4H), 1.75-1.90 (m, 4H), 2.0 (m, 2H), 2.20 (t, 2H), 2.72 (t, 2H), 3.28 (q, 2H), 5.80 (brs, 1H), 6.85 (t, 2H), 7.16 (m, 1H). LRMS: ES ⁺ m/z 396 (M+H). |
| 39 | EP274234B1, Example 35 | Prep 96 | H | | ¹ H NMR (CDCl ₃ , 300MHz) δ: 1.42 (s, 9H), 1.50 (m, 2H), 1.67 (m, 4H), 1.78-1.90 (m, 4H), 2.0 (m, 2H), 2.20 (t, 2H), 2.70 (t, 2H), 3.30 (q, 2H), 5.85 (brs, 1H), 6.92-7.05 (m, 3H). LRMS: ES ⁺ m/z 396 (M+H). |
| 40 | EP274234B1, Example 35 | Prep 98 | H | | ¹ H NMR (CDCl ₃ , 300MHz) δ: 1.41 (s, 9H), 1.48 (m, 2H), 1.53 (m, 4H), 1.75-1.90 (m, 4H), 2.0 (m, 2H), 2.18 (t, 2H), 2.63 (t, 2H), 3.28 (q, 2H), 5.71 (brs, 1H), 7.10 (dd, 2H), 7.20 (dd, 2H). LRMS: ES ⁺ m/z 444 (M+H). |
| 41 | Prep 69 | Prep 108 | (S)-methoxyethyl | | ¹ H NMR (CDCl ₃ , 300MHz) δ: 1.38-2.10 (23H, m), 2.38 (1H, m), 2.88 (2H, t), 3.27-3.38 (7H, m), 6.45 (1H, m), 7.10-7.22 (2H, m), 7.61 (1H, m), 8.54 (1H, d). |
| 42 | EP274234B1, Example 35 | Prep 117 | H | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.41 (s, 9H), 1.58 (bs, 4H), 1.72-1.82 (m, 4H), 1.86-1.92 (m, 2H), 1.96-2.05 (m, 2H), 2.10 (t, 2H), 2.54 (t, 2H), 2.83 (brs, 4H), 3.20-3.30 (m, 2H), 5.52 (brs, 1H), 6.90 (d, 1H), 7.00 (s, 1H), 7.07 (d, 1H). LRMS: TSP ⁺ m/z 400 (M+H). |

| Prep | Prec. acid | Prec. amine | R ¹ | -X-Y | Analytical Data |
|------|---------------------------|-------------|------------------|------|---|
| 43 | Prep 69 | Prep 81 | (S)-methoxyethyl | | ¹ HNMR (CDCl ₃ , 300MHz): δ: 1.39-2.08 (23H, m), 2.38 (1H, m), 2.58 (2H, t), 3.23-3.39 (7H, m), 4.23 (3H, s), 5.78 (1H, m), 6.63-6.72 (2H, m), 6.79 (1H, d). |
| 44 | Prep 69 | Prep 80 | (S)-methoxyethyl | | ¹ HNMR (CDCl ₃ , 300MHz): δ: 1.38-2.10 (23H, m), 2.39 (1H, m), 2.73 (2H, t), 3.06-3.41 (7H, m), 5.83 (1H, m), 7.19-7.35 (3H, m), 7.69-7.78 (2H, m), 7.94 (2H, d), 8.68 (1H, d). |
| 45 | EP274234B1, Example 35 | Prep 119 | H | | ¹ HNMR (CDCl ₃ , 400MHz): δ: 1.40 (s, 9H), 1.42-1.44 (m, 2H), 1.58-1.63 (m, 4H), 1.72-1.81 (m, 4H), 1.95-1.98 (m, 2H), 2.15 (t, 2H), 2.55 (t, 2H), 3.20-3.26 (m, 2H), 5.57 (brs, 1H), 7.02 (d, 2H), 7.35 (d, 2H). LRMS: ES ⁺ m/z 461 (M+Na). |
| 46 | EP274234B1, Example 35 | Prep 113 | H | | ¹ HNMR (CDCl ₃ , 400MHz): δ: 1.39-1.52 (11H, m), 1.63 (4H, m), 1.79-2.01 (6H, m), 2.18 (2H, t), 2.78 (2H, t), 3.32 (2H, q), 4.06 (3H, s), 5.61 (1H, m), 7.23 (1H, d), 7.33 (1H, d), 7.52 (1H, s), 7.90 (1H, s). |
| 47 | EP274234B1, Example 35 | Prep 90 | H | | ¹ HNMR (CDCl ₃ , 400MHz): δ: 1.35-1.50 (m, 11H), 1.62 (m, 4H), 1.72-2.02 (m, 6H), 2.18 (t, 2H), 2.72 (t, 2H), 3.31 (q, 2H), 4.21 (s, 3H), 5.60 (m, 1H), 7.12 (d, 1H), 7.41 (s, 1H), 7.63 (d, 1H), 7.80 (s, 1H). |
| 48 | EP274234B1, Example 35 | Prep 88 | H | | ¹ HNMR (CDCl ₃ , 400MHz): δ: 0.83 (t, 2H), 1.40 (s, 9H), 1.18-1.49 (m, 4H), 1.70-1.84 (m, 4H), 1.85-2.01 (m, 4H), 2.03-2.18 (m, 2H), 2.50 (t, 2H), 2.72 (t, 2H), 3.22 (q, 2H), 4.11 (t, 2H), 5.60 (brs, 1H), 6.65 (d, 1H), 6.80 (s, 1H), 6.84 (d, 1H). LRMS: M+H, 416 (ES ⁺). |

| Prep | Prec. acid | Prec. amine | R' | -X-Y | Analytical Data |
|------|---------------------------|-------------|------------------|---|---|
| 49 | EP274234B1, Example 35 | Prep 100 | H |  | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.39 (s, 9H), 1.40-1.45 (m, 2H), 1.58-1.63 (m, 4H), 1.76-1.80 (m, 4H), 1.89-1.95 (m, 2H), 2.05-2.12 (m, 2H), 2.44 (s, 3H), 2.66 (t, 2H), 3.25 (dt, 2H), 5.56 (brs, 1H), 7.07 (d, 2H), 7.15 (d, 2H). LRMS: M+Na, 428 (ES ⁺). |
| 50 | EP274234B1, Example 35 | Prep 133 | H |  | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.20 (d, 3H), 1.40 (s, 9H), 1.50-1.80 (m, 12H), 2.10 (m, 2H), 2.60 (m, 1H), 3.05 (m, 1H), 3.1 (t, 2H), 3.20 (m, 1H), 4.50 (t, 2H), 5.40 (brs, 1H), 6.65 (d, 1H), 6.90 (d, 1H), 7.0 (s, 1H). LRMS: M+H, 415.8 (TS ⁺). |
| 51 | EP274234B1, Example 35 | Prep 141 | H |  | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.10 (d, 3H), 1.40 (s, 9H), 1.45 (m, 2H), 1.60 (m, 4H), 1.65 (m, 2H), 1.80 (m, 2H), 1.90 (m, 2H), 2.10 (m, 2H), 2.50 (t, 2H), 3.10 (t, 2H), 4.00 (m, 1H), 4.50 (t, 2H), 5.40 (d, 1H), 6.60 (d, 1H), 6.85 (d, 1H), 6.95 (s, 1H). LRMS: M+H, 415.8 (TS ⁺). |
| 52 | Prep 69 | Prep 100 | (S)-methoxyethyl |  | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.40 (s, 9H), 1.41-1.43 (m, 2H), 1.56-2.00 (m, 12H), 2.26-2.36 (m, 1H), 2.42 (s, 3H), 2.58 (t, 2H), 3.21-3.28 (m, 5H), 3.30 (t, 2H), 5.73 (brs, 1H), 7.07 (d, 2H), 7.15 (d, 2H). LRMS: M+Na, 486 (ES ⁺). |
| 53 | EP274234B1, Example 35 | Prep 131 | H |  | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.42 (s, 9H), 1.44-1.55 (m, 2H), 1.58-1.70 (m, 3H), 1.75-1.88 (m, 4H), 1.90-2.01 (m, 4H), 2.18 (t, 2H), 3.35 (m, 2H), 4.27 (t, 1H), 4.62 (t, 1H), 5.72 (brs, 1H), 6.79 (dd, 1H), 6.88 (t, 1H), 7.12 (t, 1H), 7.18 (dd, 1H). LRMS: MNa ⁺ , 410 (ES ⁺). |

| Prep | Prec. acid | Prec. amine | R ¹ | -X-Y | Analytical Data |
|------|---|-------------|---------------------------|--|--|
| 54 | Prep 69 | Prep 100 | (S)-methoxy ethyl |  | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.40 (s, 9H), 1.42-1.48 (m, 2H), 1.54-1.80 (m, 9H), 1.88-2.03 (m, 4H), 2.29-2.35 (m, 1H), 2.57-2.60 (m, 2H), 3.15-3.21 (m, 4H), 3.23 (s, 3H), 3.30 (t, 2H), 4.53 (t, 2H), 6.11 (brs, 1H), 6.75 (dd, 1H), 6.90 (d, 1H), 7.01 (d, 1H). LRMS: M+Na, 482 (ES ⁺). |
| 55 | Prep 69 | Prep 90a | (S)-methoxy ethyl |  | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.40 (s, 9H), 1.50-2.00 (m, 14H), 2.10 (s, 3H), 2.30 (m, 1H), 2.50 (t, 2H), 3.10 (t, 2H), 3.20 (s, 3H), 3.30 (m, 4H), 4.50 (t, 2H), 5.70 (brs., 1H), 6.70 (s, 1H), 6.80 (s, 1H). LRMS: M+H, 474.6 (ES ⁺). |
| 56 | EP0342850, see also <i>Tet.</i> <i>Lett.</i> , 1999, 40, 2187. | Prep 76 | (S)-methoxy ethoxy methyl |  | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.41 (s, 9H), 1.57-2.03 (m, 16H), 2.58 (t, 3H), 3.32 (s, 3H), 3.11-3.57 (m, 8H), 4.53 (t, 2H), 5.98 (brs., 1H), 6.68 (d, 1H), 6.90 (d, 1H), 7.01 (s, 1H). LRMS: M+H, 490 (ES ⁺). |
| 57 | EP0342850, see also <i>Tet.</i> <i>Lett.</i> , 1999, 40, 2187. | Prep 87 | (S)-methoxy-ethoxy methyl |  | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.36 (s, 9H), 1.40 (s, 6H), 1.56-1.62 (m, 4H), 1.67-1.79 (m, 3H), 1.86-1.99 (m, 3H), 2.50-2.56 (m, 3H), 2.94 (s, 2H), 3.19-3.27 (m, 2H), 3.30 (s, 3H), 3.38 (dd, 1H), 3.43-3.45 (m, 2H), 3.50-3.54 (m, 3H), 5.92 (brs, 1H), 6.59 (d, 1H), 6.85 (d, 2H), 6.91 (s, 1H). LRMS: M+Na, 540 (ES ⁺). |
| 58 | Prep 70 | Prep 89 | (R)-methyl |  | ¹ H NMR (CDCl ₃ , 300MHz) δ: 1.10 (d, 3H), 1.35-1.52 (m, 13H), 1.53-1.63 (m, 5H), 1.65-1.95 (m, 3H), 1.96-2.15 (m, 2H), 2.33 (m, 1H), 3.25 (m, 2H), 5.85 (brs, 1H), 6.82-6.98 (m, 3H). LRMS: M+H (454) MNa ⁺ (476) ES ⁺ . |

| Prep | Prec. acid | Prec. amine | R ¹ | -X-Y | Analytical Data |
|------|--|--|---------------------------|------|--|
| 59 | Prep 69 | Prep 133 | (S)-methoxy ethyl | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.20 (d, 3H), 1.40 (s, 9H), 1.50-1.90 (m, 14H), 2.30 (m, 1H), 2.65 (m, 1H), 3.05 (m, 1H), 3.15 (t, 2H), 3.20 (m, 1H), 3.25 (s, 3H), 3.30 (t, 2H), 4.50 (t, 2H), 5.65 (brs, 1H), 6.70 (d, 1H), 6.90 (d, 1H), 7.0 (s, 1H). LRMS: M+H, 474.3 (TS ⁺). |
| 60 | Prep 69 | Prep 91 | (S)-methoxy ethyl | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.40 (s, 9H), 1.50-2.00 (m, 14H), 2.20 (s, 3H), 2.40 (m, 1H), 2.55 (t, 2H), 3.10 (m, 2H), 3.30 (m, 7H), 4.50 (t, 2H), 5.80 (brs, 1H), 6.60 (s, 1H), 6.90 (s, 1H). LRMS: M+H, 474.4 (TS ⁺). |
| 61 | EP0342850, see also Tet. Lett., 1999, 40, 2187. | J. Med. Chem., 1996, 39, 4942- 4951. | (S)-methoxy ethoxy methyl | | ¹ H NMR (CDCl ₃ , 300MHz) δ: 1.40 (s, 9H), 1.42 (m, 2H), 1.60 (m, 4H), 1.70 (m, 2H), 1.90 (m, 4H), 2.50 (m, 1H), 2.55 (t, 2H), 3.20 (m, 2H), 3.25 (s, 3H), 3.35 (m, 1H), 3.40 (m, 2H), 3.50 (m, 3H), 6.05 (brs., 1H), 7.05 (d, 2H), 7.17 (d, 2H). LRMS: M+H, 483.8 (TS ⁺). |
| 62 | Prep 69 | Prep 146 | (S)-methoxy ethyl | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.35 (s, 6H), 1.4 (s, 9H), 1.5-1.65 (m, 8H), 1.7-1.9 (m, 6H), 2.3 (m, 1H), 3.1 (q, 2H), 3.2 (t, 2H), 3.25 (s, 3H), 3.35 (t, 2H), 4.53 (t, 2H), 5.45 (brs., 1H), 6.7 (d, 1H), 7.1 (d, 1H), 7.2 (s, 1H). |
| 63 | Prep 69 | Prep 148 | (S)-methoxy ethyl | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.30-2.20 (m, 23H), 2.38 (m, 1H), 2.81 (m, 1H), 3.11-3.39 (m, 7H), 3.72 (m, 2H), 5.90 (m, 1H), 7.18 (d, 2H), 7.26 (d, 2H). |
| 64 | Prep 69 | Prep 152 | (S)-methoxy ethyl | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.41 (s, 9H), 1.26-2.02 (m, 17H), 2.26-2.38 (m, 1H), 3.00-3.11 (m, 1H), 3.12-3.22 (m, 1H), 3.26 (s, 3H), 3.27-3.39 (m, 2H), 3.65-3.73 (m, 2H), 5.97 (br.s, 1H), 7.26-7.37 (m, 4H). |

| Prep | Prec. acid | Prec. amine | R' | -X-Y | Analytical Data |
|------|------------|-------------|-------------------|------|--|
| 65 | Prep 69 | Prep 123 | (S)-methoxy ethyl | | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.20-2.00 (m, 23H), 2.34 (brm, 1H), 2.57 (t, 2H), 3.22 (s, 3H), 3.24-3.37 (m, 2H), 3.81 (s, 3H), 4.10 (q, 2H), 5.80 (brs., 1H), 6.81 (d, 1H), 7.02 (d, 1H), 7.18 (s, 1H). |
| 66 | Prep 69 | Prep 92 | (S)-methoxy ethyl | | ¹ HNMR (CDCl ₃ , 400MHz) δ: 1.39-1.46 (m, 14H), 1.56-2.02 (m, 12H), 2.30-2.46 (m, 1H), 2.55 (dd, 2H), 2.76 (dd, 1H), 3.23-3.32 (m, 8H), 4.83-4.93 (m, 1H), 5.76 (brs, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (s, 1H). LRMS: M+Na, 496 (ES ⁺). |

Alternatively Preparation 22 was prepared as follows:

To a solution of 1,1'-carbonyl diimidazole (73.9 g, 0.45 mol) in azeotropically dried isopropyl acetate (339 ml) was added the isopropyl acetate solution of the product from 5 Preparation 69 with stirring at 60 °C under an atmosphere of N₂ over a period of 1.5 hours. The transfer lines were then washed with dry isopropyl acetate (50 ml). The resultant solution was then stirred at 60 °C for a further 4.5 hours and then the reaction mixture was allowed to cool to room temperature and stirred for 15 hours. To the 10 resultant solution was then added triethylamine (46.1 g, 0.46 mol), followed by 3-(4-chlorophenyl)propylamine hydrochloride (J.Med.Chem., 1996, 39, 4942-51)(94.3 g, 0.46 mol). The resultant mixture was then heated to 60 °C for 7 hours before cooling to room temperature. Deionised water (100 ml) was then added to the reaction mixture with stirring, followed by aqueous hydrochloric acid (190 ml of a 5 M solution) until the pH of the aqueous layer was between pH 2 and 3. The aqueous layer was then separated, and 15 the organic layer was washed with aqueous potassium carbonate (50 ml of a 0.5 M solution). The aqueous phase was separated and organic phase was washed with saturated brine solution (100 ml). The aqueous layer was then separated and the organic phase was concentrated by distillation under vacuum to give the title compound as a yellow oil (200.3 g, 443 mmol, 98% yield); ¹H NMR (CDCl₃ 300MHz) δ: 1.45 (s, 9 H), 1.45-1.56 (m, 1 H), 1.56-1.74 (m, 6 H), 1.74-2.11 (m, 7 H), 2.32-2.43 (m, 1 H), 2.64 (t, 2 H), 3.22-3.30 (m, 2 H), 3.27 (s, 3 H), 3.30-3.38 (m, 2 H), 5.75-5.85 (m, br, 1 H), 7.13 (d, 2 H), 7.26 (d, 2 H); LRMS (ES positive): m/z 452 [M+H]⁺ (³⁵Cl).

Alternatively 3-(4-chlorophenyl)propylamine was prepared as follows:

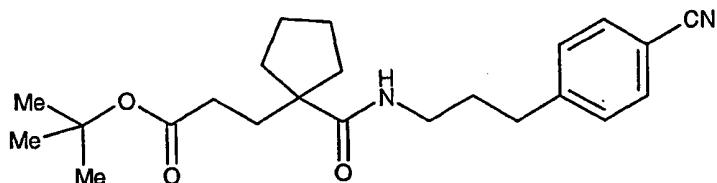
25 To a stirred solution of the starting material from stage b) below (11.3g, 62mmol) in tetrahydrofuran (500ml) was added borane dimethylsulphide complex (30ml) and the whole was refluxed for 12h. The reaction mixture was quenched with methanol (100ml), concentrated *in vacuo* and refluxed for 4h in 3M HCl (200ml). The aqueous layer was 30 concentrated to 50ml *in vacuo*, the precipitate was filtered off and dried under reduced pressure to give the title product as a white powder (10.1g, 59.7mmol, 96%); ¹HNMR (400MHz, MeOD) δ: 1.9 (quin, 2H), 2.65 (t, 2H), 2.9 (t, 2H), 7.2 (d, 2H), 7.25 (d, 2H).

Preparation of Starting Materialsa) Methyl 3-(4-chlorophenyl)propanoate

To a stirred solution of 3-(4-chlorophenyl)propanoic acid (commercially available from Maybridge) (14.5g, 77.1mmol) in methanol (400ml) was added acetyl chloride (50ml) and the reaction mixture was refluxed for 20h. After this time the reaction mixture was left to cool before being concentrated under reduced pressure. The residue was then dissolved in DCM (200ml) and washed with 1M sodium hydroxide solution (100ml). The organic layer was dried with magnesium sulphate and concentrated *in vacuo* to give the title product as a brown oil (15.7g, 77mmol, 100%); ¹HNMR (400MHz, CDCl₃) δ: 2.55 (t, 2H), 2.9 (t, 2H), 3.6 (s, 3H), 7.1 (d, 2H), 7.2 (d, 2H).

b) 3-(4-chlorophenyl)propanamide

The product from stage a) above (15g, 75.7mmol) was dissolved in methanol (400ml) before being cooled to 0°C. Ammonia gas was then bubbled through the reaction mixture for 4 hours and the reaction was left to stir for 3 days. The solvent was removed under reduced pressure and the residue was triturated with hot pentane. The remaining solid was dried *in vacuo* to give the title product as a white powder (11.32g, 61.8mmol, 82%); ¹HNMR (400MHz, CDCl₃) δ: 2.45 (t, 2H), 2.9 (t, 2H), 5.3 (bs, 1H), 5.5 (bs, 1H), 7.1 (d, 2H), 7.2 (d, 2H).

PREPARATION 67tert-Butyl-[1-({[3-(4-cyanophenyl)propyl]amino}carbonyl)cyclopentyl]acetate

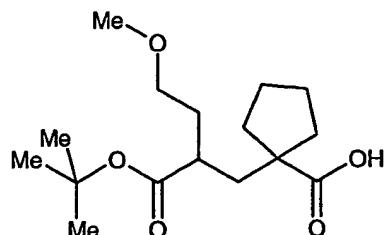
25

The product from Preparation 45 (44mg, 0.1mmol) and Cu(I)CN (13.4mg, 0.15mmol) were taken up in DMF (0.5ml) under nitrogen and stirred at ca. 130°C for 16h. After this time, a further 13mg of Cu(I)CN were added and the temperature raised to 145°C for 16h. After this time, a final 26mg of Cu(I)CN were added to the solution and the whole heated at 160°C for 24h. The reaction was quenched by the addition of water and the organics extracted with EtOAc (50ml), washed with brine and dried (MgSO₄) and evaporated to a yellow oil. This oil was subjected to preparative TLC purification using 7:3 pentane:EtOAc as eluant to give the title product, 6mg (16%); ¹HNMR (400MHz,

CDCl_3 δ : 1.40 (s, 9H), 1.45-1.49 (m, 2H), 1.62-1.64 (m, 4H), 1.79-1.83 (m, 4H), 1.94-2.00 (m, 2H), 2.12-2.17 (m, 2H), 2.65 (t, 2H), 3.22-3.35 (m, 2H), 5.65 (brs, 1H), 7.23 (d, 2H), 7.54 (d, 2H); LRMS: m/z (ES⁺) 407 (M+Na).

5 **PREPARATION 68**

1-[2-(tert-Butoxycarbonyl)-4-methoxybutyl]cyclopentanecarboxylic acid



A solution of *tert*-butyl 3-(1-carboxycyclopentyl)propanoate (12g, 49.5mmol) (see EP274234B1, Example 35) in dry tetrahydrofuran (100ml) was added to a stirred 10 solution of lithium diisopropylamide (130ml) in a mixture of hexane (52ml) and tetrahydrofuran (200ml) at -78°C under nitrogen. After 1 hour a solution of 2-bromoethyl methyl ether in tetrahydrofuran (100ml) was added maintaining the temperature at -78°C. The reaction mixture was allowed to warm up to room temperature overnight. The mixture was quenched with water (100ml) and acidified to pH 1 with 2M hydrochloric 15 acid, and extracted with ethyl acetate (2x 150ml). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo* to give the crude acid which was chromatographed on silica. Elution with increasing proportions of methanol in dichloromethane (neat dichloromethane to 1:50) gave an oil (7.7g, 25.6mmol, 52%); R_f 0.3 methanol, dichloromethane 1:20; ¹H NMR (CDCl_3 400MHz) δ : 1.4 (s, 9H), 1.4-1.7 (m, 7H), 1.75-1.95 (m, 2H), 2.0-2.15 (m, 3H), 2.3-2.4 (m, 1H), 3.3 (s, 3H), 3.3-3.4 (m, 2H); LRMS: m/z 299 (M-H⁺).

Alternatively the compound of Preparation 68 was prepared as follows:

25 To a mixture of heptane (41.2 L) and water (30.9 L) was added the product from stage b) below (5.15 kg, 12.9 mol). Dilute aqueous hydrochloric acid (2.6 L of a 5 M solution) was then added with stirring until the pH of the aqueous layer was between pH 2 and 3. The layers were separated and the aqueous phase was then extracted with heptane (20.6 L). The combined organic layers were then washed with saturated brine solution 30 (15.5 L) and were then concentrated by distillation at atmospheric pressure to give the title compound (3.90 kg, 13.0 mol, 100% yield) as a solution in heptane (total solution weight 44.0 kg). An aliquot can be taken and the solvent removed under vacuum to give

an analytical sample; ^1H NMR (CDCl_3 300MHz) δ : 1.42 (s, 9 H), 1.45-1.58 (m, 2 H), 1.58-1.70 (m, 5 H), 1.70-1.90 (m, 2 H), 2.03-2.18 (m, 3 H), 2.32-2.46 (m, 1 H), 3.27 (s, 3 H), 3.35 (t, 2 H); LRMS (EI): m/z 244 [M-C₄H₈]⁺, 227 [M-C₄H₉O]⁺, 199 [M-C₄H₉O₂C]⁺; GC (injector program: initial temp. 0 °C, rate 150 °C/min, final temp. 230 °C; oven 5 program: initial temp. 100 °C, rate 10 °C/min, final temp. 230 °C, final time 10 min; column, BP-21 25 m x 0.25mm ID x 0.25um FT; detector FID) RT 16.1 min.

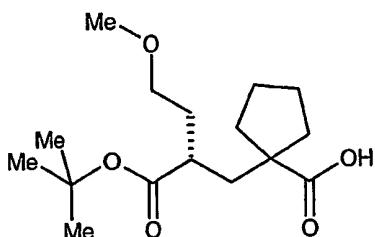
Preparation of Starting Materials

a) Crude 1-[2-(*tert*-butoxycarbonyl)-4-methoxybutyl]cyclopentanecarboxylic acid

10 To a solution of commercially supplied lithium diisopropylamide (9.63 kg of a 2M solution in tetrahydrofuran/n-heptane/ethylbenzene, 23.7 mol) in 1,2-dimethoxyethane (25 L) at -10 °C under an atmosphere of N_2 was added a solution of 1-(3-*tert*-butoxy-3-oxopropyl)cyclopentane carboxylic acid (EP274234B1 - see Example 35) (2.5 kg, 10.3 mol) in 1,2-dimethoxyethane (12.5 L) with stirring over a period of 4 hours whilst maintaining the reaction 15 temperature at -10 °C. The header tank was washed with 1,2-dimethoxyethane (2.5 L) and this was added to the reaction. The reaction mixture was then allowed to stir at -10 °C for 1.75 hours. To the resultant solution was added a solution of 2-iodoethyl methyl ether (2.73 kg, 14.4 mol) in 1,2-dimethoxyethane (10 L) over a 20 period of 1.75 hours. The reaction was then stirred at this temperature for 4 hours before warming to 20 °C over a period of 4 hours. After stirring at this temperature for 8 hours the reaction was quenched by the addition of aqueous ammonium chloride (25 L of a 2.8 M solution), ethyl acetate (12.5 L) was then added. Aqueous hydrochloric acid (10 L of 5 M solution) was then added with 25 stirring to adjust the pH to between 2 and 3. The two phases were mixed and then separated. The organic phase was then extracted three times with aqueous potassium carbonate solution (0.3 M solution; 37.5 L, 12.5 L and then 6.25 L). To the combined aqueous phases was then added n-heptane (15.6 L), and aqueous hydrochloric acid (14.5 L of a 5 M solution) with stirring until the pH of the 30 aqueous layer was between 2 and 3. The layers were then separated and the aqueous phase was extracted with n-heptane (15.6 L). The combined organic phases were then washed with saturated brine (3.1 L) and were then concentrated under vacuum to give the crude title compound (2.50 kg, 8.32 mol, 81% yield) as a solution in n-heptane (21.8 kg total solution weight).

b) Cyclohexanaminium 1-[2-(tert-butoxycarbonyl)-4-methoxybutyl] cyclopentane carboxylate

A solution of the crude product from stage a) above in n-heptane (5.51 kg, 18.3 mol in a total solution weight of 41.4 kg) was concentrated by distillation at atmospheric pressure to remove 20 L of n-heptane To the resultant solution was added cyclohexylamine (1.82 kg, 18.4 mol) as a solution in n-heptane (9.9 L) over a period of 0.5 hours. The transfer lines were then washed with n-heptane (1.1 L) and this was added to the reaction. The resultant slurry was then granulated with agitation at 22 °C for a period of 19.5 hours. The product was collected by filtration and washed with n-heptane (2 x 11.0 L) and the resultant solid was dried under vacuum at 50 °C for 20 hours. The resultant off-white solid (6.2 kg, 15.5 mol) was suspended in isopropyl acetate (37.2 L) and the resultant suspension was heated to 80 °C until a clear solution was obtained. The resultant solution was then cooled to 50 °C and a sample of authentic crystallised title compound (1.0 g) was added to seed the crystallisation. The crystallising slurry was then cooled to 20 °C over 4 hours and was then granulated at this temperature for 0.5 hours. The product was then collected by filtration and was washed with n-heptane (2 x 6.2 L) before being dried under vacuum at 45 °C for 11 hours. The resultant white solid (5.5 kg, 13.8 mol) was then suspended in isopropyl acetate (55.0 L) and was heated to 80 °C until a clear solution was obtained. The resultant solution was then cooled to 50 °C and a sample of authentic crystallised title compound (1.0 g) was added to seed the crystallisation. The crystallising slurry was then cooled to 20 °C over 4 hours and then granulated at this temperature for 22.5 hours. The product was then collected by filtration and was washed with n-heptane (2 x 5.5 L) before being dried under vacuum at 45 °C for 16.5 hours to give the title product (5.15 kg, 12.9 mol, 94% yield); m.p. (heptane) 121 °C; 1H-NMR (CDCl₃, 300 MHz), δ: 1.06-1.37 (m, 7 H), 1.42 (s, 9 H), 1.50-1.67 (m, 5 H), 1.67-1.86 (m, 5 H), 1.86-2.18 (m, 5 H), 2.30-2.58 (m, 1 H), 2.80-2.93 (m, 1 H), 3.29 (s, 3 H), 3.35 (q, 2 H), 7.29 (s, br, 3 H); Anal. found C, 66.20; H, 10.26; N, 3.50; C₂₂H₄₁NO₅ requires C, 66.13; H, 10.34; N, 3.51%.

PREPARATION 691-[(2S)-2-(*tert*-Butoxycarbonyl)-4-methoxybutyl]cyclopentanecarboxylic acid

The product from Preparation 68 and (+)-pseudoephedrine were recrystallised nine times from hexane to give a white crystalline solid. The salt was dissolved in ethyl acetate washed with 0.5M hydrochloric acid dried over magnesium sulphate and concentrated *in vacuo* the (S)-acid was obtained in 31% yield as a pale yellow oil in >90%ee by NMR analysis of the δ 3.3 peak of the (+)-pseudoephedrine salt; ^1H NMR (CDCl_3 400MHz) δ : 1.4 (s, 9H), 1.4-1.7 (m, 7H), 1.75-1.9 (m, 2H), 2.0-2.15 (m, 3H), 2.35-2.45 (m, 1H), 3.3 (s, 3H), 3.3-3.4 (m, 2H); $[\alpha]_D$ -5.2 (EtOH, c 1.2).

Alternatively Preparation 69 was prepared as follows:

To a solution of the product from Preparation 68 (3.90 kg, 13.0 mol) in heptane (58.5 L, 15 total solution weight 44.0 kg) was added (1S, 2S)-(+)-pseudoephedrine (2.13 kg, 12.9 mol) under an atmosphere of nitrogen at 20 °C. The suspension was then heated to 70 °C with stirring until a clear solution was obtained. The solution was then cooled to 40 °C and a sample of authentic crystallised title compound (0.8 g) was added to seed the crystallisation. The temperature of the mixture was maintained at 40 °C for 2 hours and 20 then the slurry was cooled to 20 °C over 6 hours. The product was then collected by filtration and was washed with heptane (2 x 2.3 L) then dried under vacuum for 22 hours at 50 °C to give (1S, 2S)-1-hydroxy-N-methyl-1-phenyl-2-propanaminium 1-[(2S)-2-(*tert*-butoxycarbonyl)-4-methoxybutyl]cyclopentane carboxylate (3.20 kg, 6.87 mol, 53% yield as an 86:14 mixture of diastereoisomeric salts as measured by ^1H NMR). The product 25 (3.20 kg, 6.87 mol) was then suspended in heptane (30 L) and heated to 70 °C until a clear solution was obtained. The resultant solution was then cooled to 58 °C and a sample of authentic crystallised title compound (1.0 g) was added to seed the crystallisation. The solution was then held at 58 °C for 1 hour and was then cooled to 20 °C over 6 hours. The slurry was then granulated at 20 °C for 12 hours. The product was 30 then collected by filtration and was washed with heptane (2 x 2 L). Drying in a vacuum oven at 50 °C for 22.5 hours gave (1S, 2S)-1-hydroxy-N-methyl-1-phenyl-2-propanaminium 1-[(2S)-2-(*tert*-butoxycarbonyl)-4-methoxybutyl]cyclopentane carboxylate

as a white crystalline solid (2.35 kg, 5.0 mol, 73% yield). m.p. (heptane); 95 °C; ¹H-NMR (CDCl₃, 300 MHz), δ: 1.08 (d, 3 H), 1.48 (s, 10 H), 1.56-1.74 (m, 4 H), 1.74-1.90 (m, 2 H), 1.90-2.03 (m, 2 H), 2.03-2.27 (m, 2 H), 2.4-2.53 (m, 1 H), 2.66 (s, 3 H), 3.08 (dq, 1 H), 3.24 (s, 3 H), 3.38 (q, 2 H), 4.58 (d, 1 H), 7.27-7.45 (m, 5 H), 7.70 (s, br, 3 H); Anal. 5 found C, 67.06; H, 9.35; N, 3.04; C₂₆H₄₃NO₆ requires C, 67.07; H, 9.31; N, 3.01%. The title compound was obtained by breaking the salt as follows. To a stirred suspension of (1S, 2S)-1-hydroxy-N-methyl-1-phenyl-2-propanaminium 1-[(2S)-2-(*tert*-butoxycarbonyl)-4-methoxybutyl]cyclopentane carboxylate (210 g, 0.45 mol) in deionised water (1.26 L) and isopropyl acetate (1.47 L) was added aqueous hydrochloric acid (99.5 ml of a 5 M 10 solution, 0.50 mol) until the pH of the aqueous layer was between pH 2 and 3. The layers were then separated, and the aqueous phase was extracted with isopropyl acetate (630 ml). The organic extracts were then combined and washed with saturated brine solution (420 ml). The organic phase was then concentrated by distillation at atmospheric pressure (to remove 1.4 L of isopropyl acetate) to give the title compound 15 as a solution in isopropyl acetate which was used directly in the next step. An aliquot can be taken and the solvent removed to give an analytical sample; ¹H NMR (CDCl₃ 300MHz) δ: 1.44 (s, 9 H), 1.48-1.59 (m, 2 H), 1.59-1.72 (m, 5 H), 1.72-1.93 (m, 2 H), 2.03-2.18 (m, 3 H), 2.35-2.46 (m, 1 H), 3.31 (s, 3 H), 3.38 (t, 2 H); LRMS (EI): m/z 244 [M-C₄H₈]⁺, 227 [M-C₄H₉O]⁺, 199 [M-C₄H₉O₂C]⁺; GC (injector program: initial temp. 0 °C, 20 rate 150 °C/min, final temp. 230 °C; oven program: initial temp. 100 °C, rate 10 °C/min, final temp. 230 °C, final time 20 min; column, BP-21 25 m x 0.25mm ID x 0.25um FT; detection FID) Retention Time 16.0 min; HPLC (column: ChiralPak AD (25 x 0.46 cm); mobile phase: hexane/IPA/acetic acid (98/2/0.1 v/v/v); Rinsing mobile phase: hexane/IPA/DEA (80/20/.5 v/v/v); flow rate: 1.0 ml/min; temperature: ambient; injection 25 volume: 20 µl; detection: ELSD) Run time: 20 mins followed by 10 mins rinse with hexane/IPA/acetic acid (98/2/0.1 v/v/v), followed by 10 mins rinse with hexane/IPA/acetic acid (98/2/0.1 v/v/v); Retention Time: minor enantiomer 15.5 min (3.3%), major enantiomer 17.5 min (96.7%).

30 Alternatively the product from Preparation 69 was prepared by asymmetric hydrogenation using a number of catalysts and conditions as follows.

i) Hydrogenation 1

The starting material from stage c) below (62 mg, 0.21 mmol) and [(*R*)-(+)-2,2'- 35 bis(diphenylphosphino)-1,1'-binaphthylchloro(*para*-cymene)] ruthenium chloride (*J. Org. Chem.* 1994, 59, 3064-76) (2.0 mg, 0.0021 mmol) were charged to the pressure vessel.

The vessel was purged with nitrogen by pressurising to 10 bar and then venting. This purging procedure was then repeated a further 4 times. Degassed methanol (2 ml) was then added. The vessel was pressurised with hydrogen (10 bar), then vented and pressurised again with hydrogen (10 bar). The mixture was stirred at 65°C (oil bath temperature) for 18h. After cooling to room temperature, the pressure was released and the solvent was removed under reduced pressure to give the title compound as an oil, HPLC (column: ChiralPak AD (25 x 0.46 cm); mobile phase: hexane/IPA/acetic acid (98/2/0.1 v/v/v); rinsing mobile phase: hexane/IPA/DEA (80/20/0.5 v/v/v); flow rate: 1.0 ml/min; temperature: ambient; injection volume: 20 µl; detection: ELSD) Run time: 20 mins followed by 10 mins rinse with hexane/IPA/acetic acid (98/2/0.1 v/v/v), followed by 10 mins rinse with hexane/IPA/acetic acid (98/2/0.1 v/v/v); retention Time: *R* enantiomer 15.5 min, *S* enantiomer 17.5 min; 91% conversion, *S*-enantiomer, ee 97%.

ii) Hydrogenation 2

The starting material from stage c) below (82 mg, 0.27 mmol), sodium *tert*-butoxide (25 mg, 0.26 mmol) and [(S)-3,3',4,4',5,5'-hexamethyl(6,6'-diphenyl)-2,2'-diyl]bis(diphenylphosphino)ruthenium bis(trifluoroacetate) (see WO01/94359) (2.5 mg, 0.0027 mmol) were charged to the pressure vessel. The vessel was purged with nitrogen by pressurising to 10 bar and then venting. This purging procedure was then repeated a further 4 times. Degassed methanol (2 ml) was then added. The vessel was pressurised with hydrogen (10 bar), then vented and pressurised again with hydrogen (10 bar). The mixture was then stirred at 65°C for 18h. The vessel was then allowed to cool to room temperature and the pressure was then released. To the reaction mixture was then added ethyl acetate/heptane (1:1, 10 ml) and hydrochloric acid (1M, 5 ml). The organic phase was separated and dried over magnesium sulfate and the solvent was removed under reduced pressure to give the title compound as an oil, HPLC (column: ChiralPak AD (25 x 0.46 cm); mobile phase: hexane/IPA/acetic acid (98/2/0.1 v/v/v); Rinsing mobile phase: hexane/IPA/DEA (80/20/0.5 v/v/v); flow rate: 1.0 ml/min; temperature: ambient; injection volume: 20 µl; detection: ELSD) Run time: 20 mins followed by 10 mins rinse with hexane/IPA/acetic acid (98/2/0.1 v/v/v), followed by 10 mins rinse with hexane/IPA/acetic acid (98/2/0.1 v/v/v); Retention Time: *R* enantiomer 15.5 min, *S* enantiomer 17.5 min; >98%conversion, *R*-enantiomer, ee 91%.

iii) Hydrogenation 3

Using the same method as described for Hydrogenation 2 above but using [(*R*)-(6,6'-dimethoxybiphenyl-2,2'-diyl)bis(diphenylphosphino)] ruthenium bis (trifluoroacetate)

(EP398132) as the pre-catalyst gave the title compound as an oil, HPLC (column: ChiralPak AD (25 x 0.46 cm); mobile phase: hexane/IPA/acetic acid (98/2/0.1 v/v/v); Rinsing mobile phase: hexane/IPA/DEA (80/20/.5 v/v/v); flow rate: 1.0 ml/min; temperature: ambient; injection volume: 20 μ l; detection: ELSD) Run time: 20 mins

5 followed by 10 mins rinse with hexane/IPA/acetic acid (98/2/0.1 v/v/v), followed by 10 mins rinse with hexane/IPA/acetic acid (98/2/0.1 v/v/v); Retention Time: *R* enantiomer 15.5 min, *S*-enantiomer 17.5 min; 57% conversion, *S*-enantiomer, ee >98%.

iv) Hydrogenation 4

10 The starting material from stage i) below (80 mg, 0.25 mmol) and [(*R*)-(-)-4,12-bis(diiisopropylphosphino)-[2.2]-paracyclophano-(1,5-cyclooctadiene)] rhodium (I) tetrafluoroborate (*J. Am. Chem. Soc.* 1997, 119, 6207-6208) (1.8 mg, 0.0025 mmol) were charged to a pressure vessel. The vessel was then purged with nitrogen by pressurising to 10.5 bar and then venting. This purging procedure was then repeated a further 4 times. Degassed methanol (2 ml) was then added. The vessel was pressurised with hydrogen (10.5 bar), then vented and pressurised again with hydrogen (10.5 bar). The mixture was then stirred at room temperature for 18h and the pressure was then released. To the reaction mixture was added *tert*-butyl methyl ether and 2M hydrochloric acid and the phases were mixed. The organic phase was separated, dried over magnesium sulfate, and the solvent was removed under reduced pressure to give the title compound as an oil, HPLC (column: ChiralPak AD (25 x 0.46 cm); mobile phase: hexane/IPA/acetic acid (98/2/0.1 v/v/v); Rinsing mobile phase: hexane/IPA/DEA (80/20/.5 v/v/v); flow rate: 1.0 ml/min; temperature: ambient; injection volume: 20 μ l; detection: ELSD) Run time: 20 mins followed by 10 mins rinse with hexane/IPA/acetic acid (98/2/0.1 v/v/v), followed by 10 mins rinse with hexane/IPA/acetic acid (98/2/0.1 v/v/v); Retention Time: *R* enantiomer 15.5 min, *S* enantiomer 17.5 min; >98% conversion, *R*-enantiomer, ee 91%.

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v) Hydrogenation 5

30 The starting material from stage i) below (80 mg, 0.25 mmol) and [(*S*)-3,3',4,4',5,5'-hexamethyl(6,6'-diphenyl)-2,2'-diyl]bis(diphenylphosphino)ruthenium bis(trifluoroacetate) (see WO 01/94359) (2.3 mg, 0.0025 mmol) were charged to the pressure vessel. The vessel was purged with nitrogen by pressurising to 10.5 bar and then venting. This purging procedure was then repeated a further 4 times. Degassed methanol (2 ml) was then added. The vessel was pressurised with hydrogen (10.5 bar), then vented and pressurised again with hydrogen (10.5 bar). The mixture was stirred at 45°C for 18h and

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then allowed to cool to room temperature. The pressure was then released and to the reaction mixture was added *tert*-butyl methyl ether and 2M hydrochloric acid and the phases were mixed. The organic phase was separated and dried over magnesium sulfate, and the solvent was then removed under reduced pressure to give the title compound as an oil, HPLC (column: ChiralPak AD (25 x 0.46 cm); mobile phase: hexane/IPA/acetic acid (98/2/0.1 v/v/v); Rinsing mobile phase: hexane/IPA/DEA (80/20/0.5 v/v/v); flow rate: 1.0 ml/min; temperature: ambient; injection volume: 20 μ l; detection: ELSD) Run time: 20 mins followed by 10 mins rinse with hexane/IPA/acetic acid (98/2/0.1 v/v/v), followed by 10 mins rinse with hexane/IPA/acetic acid (98/2/0.1 v/v/v); Retention Time: *R* enantiomer 15.5 min, *S* enantiomer 17.5 min; >98% conversion, *R*-enantiomer, ee 97%.

vi) Hydrogenation 6

The starting material from stage i) below (80 mg, 0.25 mmol) and [(*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] ruthenium bis(trifluoroacetate)] (2.4 mg, 0.0025 mmol) or [(*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthylchloro(*para*-cymene)] ruthenium chloride (*J. Org. Chem.* 1994, 59, 3064-76) (2.4 mg, 0.0025 mmol) were charged to the pressure vessel. Using the same procedure as described in preparation 6 gave the title compound as an oil; HPLC (column: ChiralPak AD (25 x 0.46 cm); mobile phase: hexane/IPA/acetic acid (98/2/0.1 v/v/v); Rinsing mobile phase: hexane/IPA/DEA (80/20/0.5 v/v/v); flow rate: 1.0 ml/min; temperature: ambient; injection volume: 20 μ l; detection: ELSD) Run time: 20 mins followed by 10 mins rinse with hexane/IPA/acetic acid (98/2/0.1 v/v/v), followed by 10 mins rinse with hexane/IPA/acetic acid (98/2/0.1 v/v/v); Retention Time: *R* enantiomer 15.5 min, *S* enantiomer 17.5 min; >98% conversion, *S*-enantiomer, ee >98%.

vii) Hydrogenation 7

The starting material from stage i) below (80 mg, 0.25 mmol) and [(*R*)-(6,6'-dimethoxybiphenyl-2,2'-diyl)bis(diphenylphosphino)] ruthenium bis (trifluoroacetate) (EP398132) (2.3 mg, 0.0025 mmol) were charged to the pressure vessel. Using the same procedure as described in hydrogenation 6 gave the title compound as an oil HPLC (column: ChiralPak AD (25 x 0.46 cm); mobile phase: hexane/IPA/acetic acid (98/2/0.1 v/v/v); Rinsing mobile phase: hexane/IPA/DEA (80/20/0.5 v/v/v); flow rate: 1.0 ml/min; temperature: ambient; injection volume: 20 μ l; detection: ELSD) Run time: 20 mins followed by 10 mins rinse with hexane/IPA/acetic acid (98/2/0.1 v/v/v), followed by

10 mins rinse with hexane/IPA/acetic acid (98/2/0.1 v/v/v); Retention Time: *R* enantiomer 15.5 min, *S* enantiomer 17.5 min; >98% conversion, *S*-enantiomer, ee >98%.

Preparation of starting materials

5 a) 1-(2-*tert*-Butoxycarbonyl-4-methoxy-3-oxo-butyl)-cyclopentane carboxylic acid
A solution of diisopropylamine (35.0 ml, 250 mmol) in THF (70 ml) was cooled to -15°C under nitrogen. *n*-Butyllithium (2.5 M, 100 ml, 250 mmol) was then added dropwise, whilst maintaining the temperature below -10 °C. To the resultant solution was added a solution of 1-(3-*tert*-butoxy-3-oxopropyl)cyclopentane carboxylic acid (see EP274234B1, example 35) (27.52 g, 113.6 mmol) in THF (50 ml) and the reaction was then stirred at -10 to -15 °C for 1h. To the reaction mixture was then added a solution of methyl methoxyacetate (18.0 ml) in THF (20 ml), and the resultant mixture was then allowed to warm to room temperature and then stirred for 19 hours. To the reaction mixture was added *tert*-butyl methyl ether (300 ml) and deionised water (300 ml), and the aqueous phase was then acidified with 2M hydrochloric acid to pH 3 with stirring. The phases were separated and the aqueous phase was then extracted with *tert*-butyl methyl ether (250 ml). The combined organic phases were then washed with water (250 ml) and then brine (250 ml), dried over magnesium sulfate, and the solvent was then removed under reduced pressure. The crude title compound was then purified by flash chromatography on silica gel using ethyl acetate/ heptane (1:2 to 1:1) as the eluent to give the title compound (17.35 g, 55.2 mmol, 49% yield); ¹H NMR (400 MHz, CDCl₃) δ: 1.43 (s, 9 H), 1.69-1.47 (m, 6 H), 2.17-2.05 (m, 2 H), 2.18 (dd, 1 H), 2.32 (dd, 1 H), 3.42 (s, 3 H), 3.59 (t, 1 H), 4.17 (q, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ: 24.7, 27.8, 34.9, 35.8, 36.7, 53.2, 53.3, 59.2, 82.3, 168.3, 183.4, 203.2.

10 b) 8-Methoxymethyl-6-oxo-7-oxa-spiro[4.5]decane-9-carboxylic acid *tert*-butyl ester
A solution of the product from stage a) above (10.50 g, 33.4 mmol) in methanol (100 ml) was cooled to 0 to -5°C under nitrogen. To the resultant solution was then added sodium borohydride (2.02 g, 53.4 mmol) in portions, keeping the temperature below 0 °C. The reaction was then stirred for 1 hour. Ethyl acetate (150 ml) and water (150 ml) were then added, and the aqueous phase was acidified by adding hydrochloric acid (50 ml of a 2 M solution) with stirring. The phases were then separated and the aqueous phase was extracted with ethyl acetate (100 ml). The combined organic phases were then washed with water (50 ml) and then brine (50 ml). The combined aqueous washings were then

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extracted with ethyl acetate (100 ml). The combined ethyl acetate extracts were then dried over magnesium sulfate and the solvent was then removed under reduced pressure to give a pale yellow oil (11.29 g), that was used in the next step without further purification. A portion of this oil (10.89 g, 34.4 mmol) was dissolved in THF (100 ml) under nitrogen, and to the resultant solution was added dicyclohexylcarbodiimide (7.10 g, 34.4 mmol). The mixture was then stirred at room temperature for 19 hours. To the reaction was then added methanol (5 ml) and acetic acid (2 ml) and the mixture was then stirred for 30 minutes. The solvent was then removed under reduced pressure. The crude product was then suspended in ethyl acetate (50 ml) and the reaction by-products were removed by filtration. The filter cake was washed with ethyl acetate (50 ml) and the filtrate was then concentrated under reduced pressure. The crude title compound was then purified by flash chromatography on silica gel using ethyl acetate/heptane (1:3 to 2:3) as the eluent to give the title compound as a 2:1 mixture of diastereoisomers (8.19 g, 27.4 mmol, 80%); For analytical purposes a sample was purified by flash chromatography on silica gel using EtOAc/heptane (1:2) as the eluent; i) Higher rf spot (single diastereoisomer); ¹H NMR (400 MHz, CDCl₃) δ: 1.47 (s, 9 H), 1.50-2.15 (m, 9 H), 2.30 (m, 1 H), 2.90 (td, 1 H), 3.38 (s, 3 H), 3.58 (d, 2 H), 4.62 (dt, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ ppm 25.5, 25.8, 28.0, 36.9, 38.3, 39.6, 39.6, 40.4, 47.8, 59.5, 73.1, 79.5, 81.8, 171.3, 176.5; ii) Lower rf spot (not completely separated, 3.5:1 mixture of diastereoisomers); ¹H NMR (400 MHz, CDCl₃) δ: (major isomer) 1.47 (s, 9 H), 1.49-2.10 (m, 8 H), 2.18 (dd, 1 H), 2.43 (m, 1 H), 3.03 (m, 1 H), 3.35 (s, 3 H), 3.60-3.67 (m, 2 H), 4.72 (q, 1 H).

25 c) 1-(2-tert-Butoxycarbonyl-4-methoxy-but-2E-enyl)-cyclopentane carboxylic acid
To a solution of the product from stage b) above (6.11 g, 20.49 mmol) in toluene (50 ml) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (3.7 ml, 24.58 mmol), and the resultant solution was then heated at reflux under nitrogen for 5 h. The solution was then cooled to room temperature and the solvent was removed under reduced pressure. To the resultant residue was then added deionised water (100 ml) and the mixture was then extracted with *tert*-butyl methyl ether (30 ml). The phases were then separated and the aqueous phase was acidified to pH 2 with hydrochloric acid (15 ml of a 2 M solution) and then extracted with *tert*-butyl methyl ether (2 × 30 ml). The combined organic extracts were then washed with water (30 ml) and then brine (30 ml) and dried over magnesium sulfate. The solvent was then removed under reduced pressure to give the crude title

compound (6.29 g), which was then crystallised from heptane (15 ml) at 0 °C. The resultant solid was collected by filtration was then washed with ice-cold heptane (2 × 5 ml) to give the title compound as a white solid (1.79 g, 6.0 mmol, 29%, *E*-isomer assigned on basis of chemical shifts); ¹H NMR (400 MHz, CDCl₃) δ: 1.47 (s, 9 H), 1.45-1.70 (m, 6 H), 2.05-2.10 (m, 2 H), 2.74 (s, 2 H), 3.36 (s, 3 H), 4.09 (d, 2 H), 6.75 (t, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ: 23.9, 28.0, 34.1, 35.0, 55.0, 58.6, 69.2, 80.8, 132.7, 139.1, 167.1, 183.3.

10 The filtration liquors were concentrated to give a yellow oil (4.02 g). This mixture was purified by flash chromatography on silica gel using ethyl acetate/ heptane (1:2 + 0.5% acetic acid) as the eluent to give more of the title compound and a colourless oil (2.43 g, 1.1:1 *E/Z* ratio); 1-(2-*tert*-Butoxycarbonyl-4-methoxy-but-2Z-enyl)-cyclopentane carboxylic acid: ¹H NMR (400 MHz, CDCl₃) δ: (key signals) 1.48 (s, 9 H), 2.65 (s, 2 H) 3.33 (s, 3 H), 4.29 (d, 2 H), 5.99 (t, 1 H).

15 A sample of the vinyl ether 1-[(3*E*)-2-(*tert*-butoxycarbonyl)-4-methoxy-3-but enyl]cyclopentanecarboxylic acid was also isolated by flash chromatography (*E* geometry assigned on basis of coupling constant): ¹H NMR (400 MHz, CDCl₃) δ: 1.42 (s, 9 H), 1.40-1.70 (m, 6 H) 2.03 (d, 2 H), 2.06 (m, 1 H), 2.17 (m, 1 H), 2.83 (s, 1 H), 3.49 (s, 3 H), 4.66 (dd, 1 H), 6.35 (d, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ: 24.9, 25.2, 28.4, 34.7, 38.8, 41.7, 44.3, 53.5, 56.1, 80.9, 101.9, 149.2, 174.5, 184.5.

d) 1-Benzyl 3-*tert*-butyl 2-(2-methoxyethyl)malonate

25 To a stirred suspension of sodium hydride (14.4 g of a 60% dispersion in mineral oil, 360 mmol) in THF (300 ml) was cooled to 0 °C under nitrogen. To the resultant slurry was added, over a period of 45 minutes, a solution of benzyl-*tert*-butyl malonate (90.0 g, 360 mmol) in THF (500 ml). The reaction mixture was allowed to warm to room temperature and was then stirred for 1 hour. The reaction mixture was then cooled to 0 °C again, and a solution of 2-bromoethyl methyl ether (50.0 g, 360 mmol) in THF (100 ml) was then added over a period of 0.5 hours. The reaction was then allowed to warm to room temperature and left to stir for 19 hours. The reaction was then brought to reflux for 24 hours before cooling to room temperature. To the reaction mixture was added deionised water (500 ml) and the product was then extracted with ethyl acetate (3 × 500 ml). The organic phases were combined, dried over magnesium sulfate and were then

concentrated by distillation under reduced pressure to give the product as a crude oil (100 g). The product was then purified by column chromatography on silica gel using 10% diethyl ether in heptane then 20% diethyl ether in heptane as the eluent, to give the title compound as an oil (37.1 g, 120 mmol, 33% yield);
5 TLC (diethyl ether/heptane 3:7, visualised with Dragendorff's dip) R_f 0.25; 1H NMR (300 MHz, $CDCl_3$) δ : 1.4 (s, 9 H), 2.13 (dt, 2 H), 3.30 (s, 3 H), 3.43 (t, 2 H), 3.51 (t, 1 H), 5.20 (d, 2 H), 7.29-7.40 (m, 5 H).

e) 2-(*tert*-Butoxycarbonyl)-4-methoxybutanoic acid
10 To a solution of the product from stage d) above (37.1 g, 120 mmol) in dioxane (740 ml) and water (111 ml) was added potassium hydroxide (6.73 g, 120 mmol) with stirring. The resultant solution was then stirred at room temperature for 19 hours. The solvent was then removed by distillation under reduced pressure and the resulting concentrate was diluted with deionised water (300 ml). The aqueous solution was then washed with diethyl ether (3 x 400 ml). To the aqueous phase was then added 1 M hydrochloric acid until the pH was 2. The acidified solution was then extracted with ethyl acetate (3 x 400 ml) and the combined organic layers were then dried over magnesium sulfate. The solvent was removed by distillation under reduced pressure to give the title compound as an oil (14.7 g, 67.4 mmol, 56% yield); TLC (diethyl ether/heptane 3:7, visualised with Dragendorff's dip) R_f 0.20; 1H NMR (300 MHz, $CDCl_3$) δ : 1.48 (s, 9 H), 2.16 (dt, 2 H), 3.16 (s, 3 H), 3.27-3.51 (m, 3 H).

f) *tert*-Butyl 2-(2-methoxyethyl)acrylate
25 To a solution of the product from stage e) above (20.8 g, 95.3 mmol) in pyridine (170 ml) was added piperidine (1.70 ml, 19.1 mmol), followed by paraformaldehyde (3.89g, 130 mmol). The resultant mixture was then heated at 63 °C for 3.5 hours. The reaction mixture was then allowed to cool to room temperature and stirred for 19 hours. The solvent was then removed by distillation under reduced pressure. To the concentrate was then added deionised water (250 ml) followed by hydrochloric acid (200 ml of a 2 M solution). The aqueous phase was then extracted with diethyl ether (1 x 350 ml, followed by 2 x 400 ml). The combined organic extracts were then washed with hydrochloric acid (400 ml of a 2 M solution) and dried over magnesium sulfate.
30 Removal of the solvent under reduced pressure gave the title compound as an oil. 1H NMR (300 MHz, $CDCl_3$) δ : 1.50 (s, 9 H), 2.56 (t, 2 H), 3.35 (s, 3 H), 3.46-
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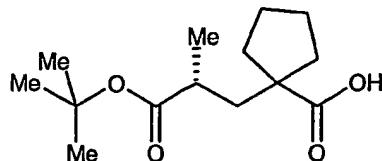
3.53 (m, 2 H), 5.54 (s, 1 H), 6.13 (s, 1 H); LRMS (EI): m/z 130 [M-C₄H₈]⁺, 113 [M-C₄H₉O]⁺.

g) tert-Butyl (2E)-2-(2-methoxyethyl)-3-[(4-methylphenyl)sulfonyl]-2-propenoate
5 To a stirred solution of *para*-toluenesulfonyl iodide (J. Chem. Soc. Perkin Trans. 1, 1988, 1029) (11.4 g, 40.2 mmol) in dichloromethane (25.0 ml) was added a solution of the product from stage f) above (5.0 g, 26.8 mmol) in dichloromethane (10 ml) at room temperature under nitrogen. The resultant solution was then stirred for 60 hours. The reaction mixture was then cooled to 0 °C and
10 triethylamine (5.4 g, 53.4 mmol) was then added over a period of 15-20 minutes whilst maintaining the temperature at 0 °C. The resultant mixture was then stirred at 0 °C for 0.5 hours before then warming to room temperature and stirring for a further 5 hours. The reaction was then quenched by the addition of deionised water (100 ml) and the layers were then separated. The aqueous phase was then
15 extracted with dichloromethane (100 ml) and the organic extracts were combined and washed with hydrochloric acid (50 ml of a 1 M solution). The organic layer was then washed with aqueous sodium thiosulfate (100 ml of a 5% w/v solution) and then with deionised water (100 ml). The organic layer was then dried over magnesium sulfate and the solvent was removed under reduced pressure to give
20 the crude product as a dark oil (7.5 g, 22.0 mmol, 82% yield). This reaction was repeated twice more using the same conditions and the combined crude products (74.6 g) were then purified by flash chromatography on silica gel using heptane/ethyl acetate (4:1) as the eluent to give the title compound as a white crystalline solid (48.0 g); m.p. (heptane/ethyl acetate) 84-86 °C; TLC (ethyl
25 acetate/heptane 1:4, visualised with UV @ 254 nm) R_f 0.20; ¹H NMR (300 MHz, CDCl₃) δ ppm 1.45 (s, 9 H), 2.48 (s, 3 H), 3.14 (t, 2 H), 3.30 (s, 3 H), 3.51 (t, 2 H), 7.10 (s, 1 H), 7.35 (d, 2 H), 7.83 (d, 2 H).

h) 1-[(1E)-2-(tert-Butoxycarbonyl)-4-methoxy-1-buteneyl]cyclopentane carboxylic acid
30 To a stirred solution of lithium diisopropylamide (64.6 ml of a 2 M solution in THF/heptane/ethyl benzene) in anhydrous THF (200 ml) at 0 °C was added a solution of cyclopentane carboxylic acid (7.0 ml, 58.7 mmol) in anhydrous THF (100 ml) over a period of 10 minutes under nitrogen. The reaction was then allowed to warm to room temperature whilst stirring for 2.5 hours. The resultant
35 slurry was then cooled to 0 °C and zinc chloride (38.2 ml of a 1 M solution in diethyl ether) was then added over a period of 1 minute. The reaction mixture

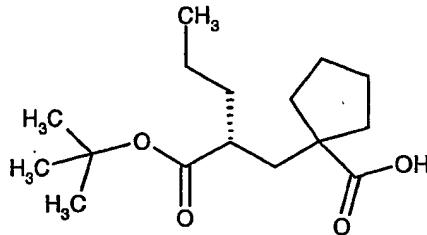
was then stirred for 10 minutes, and to the resultant solution was added a solution of the product from stage g) above (20.0 g, 58.7 mmol) in anhydrous THF (160 ml) over a period of 5 minutes). The reaction mixture was then stirred for 2 hours whilst maintaining the temperature between 0 to 5°C. The reaction 5 was then allowed to warm to room temperature and stirred for 19 hours. The reaction was then quenched by the addition of isopropanol (120 ml) and the mixture was then stirred for 1 hour. The reaction mixture was filtered, and the solid by-products were then washed with THF (10 ml). To the filtrate was then added deionised water (400 ml), aqueous sodium hydroxide (200 of a 1 M 10 solution) and ethyl acetate (600 ml). More deionised water was added (600 ml), and the resultant solid was removed by filtration. The layers were then separated, and to the aqueous phase was then added hydrochloric acid (1 M solution) until the pH was 2. The aqueous phase was then extracted with ethyl acetate (2 x 700 ml), the organic layers were combined, dried over magnesium sulfate and then 15 the solvent was removed by distillation under reduced pressure to give the crude product as a yellow oil (16.7 g). The product was then purified by flash chromatography on silica gel using dichloromethane/methanol (9:1) as the eluent to give the title compound as a yellow oil (15.2 g, 50.9 mmol, 87% yield); TLC (dichloromethane/methanol 9:1, visualised with UV @ 254 nm) R_f 0.70; ^1H NMR (300 MHz, CDCl_3) δ ppm 1.48 (s, 9 H), 1.67-1.90 (m, 6 H), 2.37-2.48 (m, 2 H), 2.58 (t, 2 H), 3.32 (s, 3 H), 3.48 (t, 2 H), 6.83 (s, 1 H); LRMS (ES negative): m/z 20 253 [M- CO_2H]⁻.

i) Sodium 1-[(1*E*)-2-(*tert*-butoxycarbonyl)-4-methoxy-1-butenyl] cyclopentane carboxylate
25 To a stirred solution of the product from stage h) above (15.0 g, 50.3 mmol) in isopropyl acetate (300 ml) was added sodium methoxide (3.0 g, 55.6 mmol). The resultant suspension was then stirred for 19 hours at room temperature. The solid was collected by filtration under vacuum and washed with isopropyl acetate 30 before drying in a vacuum oven at 50 °C for 19 hours to give the title compound as a white solid (10.0 g, 31.2 mmol, 62% yield); m.p. (isopropyl acetate) 195-198 °C; ^1H NMR (300 MHz, CDCl_3) δ ppm 1.48 (s, 9 H), 1.51-1.72 (m, 6 H), 2.21-2.37 (m, 2 H), 2.61 (t, 2 H), 3.34 (s, 3 H), 3.51 (t, 2 H), 6.86 (s, 1 H); LRMS (ES negative): m/z 253 [M- CO_2Na]⁻.

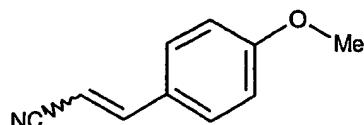
PREPARATION 701-[(2R)-3-*tert*-Butoxy-2-methyl-3-oxopropyl]cyclopentanecarboxylic acid

The title compound was prepared according to similar methods to Preparations 68 and 5 69, using methyl iodide in place of 2-bromoethylmethyl ether. Its (+)-pseudoephedrine salt was recrystallised three times from hexane. The title compound was obtained in 28% yield as a pale yellow oil in >95%ee by NMR analysis of the δ 1.4 peak of the (+)-pseudoephedrine salt; ^1H NMR (CDCl_3 400MHz) δ : 1.13 (d, 3H), 1.40-1.60 (m, 11H), 1.60-1.78 (m, 5H), 2.14 (m, 3H), 2.38 (m, 1H); $[\alpha]_D$ -24.2 (EtOH, c 1.2).

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PREPARATION 711-[(2R)-2-(*tert*-Butoxycarbonyl)-4-pentyl]-cyclopentane carboxylic acid

A mixture of (R)-1-[2-(*tert*-butoxycarbonyl)-4-pentenyl]-cyclopentane carboxylic acid (WO 15 9113054, Example 10) (10g, 35.4mmol) and 10% palladium on charcoal (600mg) in dry ethanol (25ml) was hydrogenated at 1 atm. and room temperature for 18 hours. The reaction mixture was filtered through Arbocel®, and the filtrate evaporated under reduced pressure to give the title compound as a yellow oil, 9.6g, 95%; ^1H NMR (CDCl_3 , 0.86 (t, 3H), 1.22-1.58 (m, 15H), 1.64 (m, 4H), 1.78 (dd, 1H), 2.00-2.18 (m, 3H), 2.24 (m, 1H); $[\alpha]_D$ = -3.3° (c = 0.09, ethanol).

PREPARATION 723-(4-Methoxyphenyl)-2-propenenitrile

25

A solution of 4-iodoanisole (1g, 4.2mmol), acrylonitrile (0.3ml, 4.7mmol), *tri-*o*-tolylphosphine* (243mg, 0.4mmol), palladium (II) acetate (90mg, 0.4mmol) and

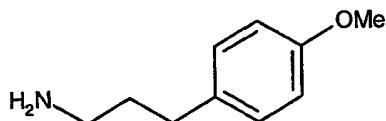
triethylamine (1.78ml, 12mmol) in acetonitrile (20ml) was refluxed under nitrogen for 14 hours. The reaction mixture was diluted with EtOAc (50ml) and washed with 2M sodium hydrogen carbonate (100 ml), the organic layer was dried over magnesium sulphate and filtered. The filtrate was evaporated *in vacuo* and purified by column

5 chromatography using pentane, then 95:5 pentane:ethyl acetate, then 90:10 pentane:ethyl acetate to give the title compound (414mg, 2.5mmol) as a mixture of *cis* and *trans* isomers as yellow crystals, ^1H NMR (CDCl_3 400MHz) δ : 3.8 (s, 3H), 5.7 (d, 1H), 6.9 (d, 1H), 7.2 (d, 1H), 7.4 (d, 2H); LRMS: m/z 176 ($\text{M}+\text{NH}_4^+$); Anal. Found C, 74.44; H, 5.66; N, 8.36. $\text{C}_{10}\text{H}_{39}\text{NO}\cdot 0.1\text{H}_2\text{O}$ requires C, 74.42; H, 5.65; N, 8.41%.

10

PREPARATION 73

3-(4-Methoxyphenyl)-1-propanamine



15 A solution of the product from preparation 72 (414mg, 2.6mmol) in ammonium hydroxide solution (10ml) and ethanol (10ml) was shaken under hydrogen at 40 p.s.i. with Ra-Ni (100mg) for 12 hours. The reaction mixture was filtered through arbocel and washed with ethanol (20 ml), the filtrate was evaporated *in vacuo* to give the title compound (183mg, 1.1mmol) as a yellow oil; ^1H NMR (CDCl_3 400MHz) δ : 1.7 (bs, 2H), 2.0 (bs, 2H), 2.5 (t, 2H), 2.7 (bs, 2H), 3.7 (s, 3H), 6.7 (d, 2H), 7.0 (d, 2H); LRMS: m/z 376 ($\text{M}+\text{H}^+$).

20

25 The following compounds of formula (IIIa), i.e. compounds of general formula III where X is $-(\text{CH}_2)_3-$, were prepared by methods similar to those described in Preparations 72 and 73 from the precursors indicated.

25



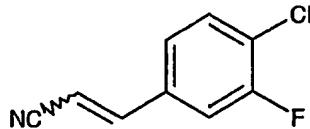
(IIIa)

Table 3

| Prep | Prec | Y | Analytical Data |
|------|---|---|---|
| 74 | 1-bromo-4-ethyl benzene (Aldrich Chemical Co) | | ^1H NMR (CD_3OD , 400MHz) δ : 1.1 (bs, 3H), 1.7 (bs, 2H), 2.6 (bs, 5H), 3.4 (bs, 1H), 7.1 (bs, 4H). LRMS: m/z 164 ($\text{M}+\text{H}^+$). |

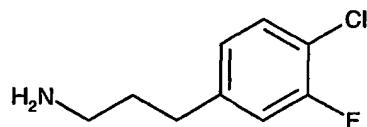
| Prep | Prec | Y | Analytical Data |
|------|--|---|---|
| 75 | 4-bromo-3-methyl-anisole (Lancaster) | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.7 (m, 2H), 2.25 (s, 3H), 2.58 (m, 2H), 2.7 (m, 2H), 3.72 (d, 3H), 6.65 (m, 2H), 7.01 (m, 1H). LRMS: m/z 180 (M+H ⁺). |
| 76 | 5-iodo-2,3-dihydrobenzofuran (Maybridge Chemicals) | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.8 (m, 2H), 2.6 (t, 2H), 2.7 (t, 2H), 3.1 (m, 2H), 3.3 (t, 2H), 4.5 (t, 1H), 6.6 (d, 1H), 6.9 (d, 1H), 7.1 (s, 1H). |
| 77 | 2,4-difluoro-iodobenzene (Aldrich Chemical Co.) | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.64 (m, 2H), 2.6 (t, 2H), 2.7 (t, 2H), 6.7 (m, 2H), 7.1 (m, 1H). LRMS: m/z 172.1 (M+H). |
| 78 | 2-bromonaphthalene (Aldrich Chemical Co.) | | ¹ H NMR (MeOD, 400MHz) δ: 2.0 (m, 2H), 2.9 (m, 4H), 7.4 (m, 3H), 7.6 (m, 1H), 7.7 (m, 3H). LRMS: m/z (ES ⁺) 186 (M+H). |
| 79 | 1-bromonaphthalene (Aldrich Chemical Co.) | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 2.1 (m, 2H), 3.0 (m, 2H), 3.1 (m, 2H), 7.3 (m, 2H), 7.5 (m, 2H), 7.7 (m, 1H), 7.8 (m, 1H). LRMS: m/z (ES ⁺) 186 (M+H). |
| 80 | Prep 114 | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.78-1.88 (m, 2H), 2.68-2.83 (m, 4H), 7.19-7.36 (m, 3H), 7.70-7.77 (m, 2H), 7.92 (d, 2H), 8.69 (d, 1H). |
| 81 | 3,4-ethylenedioxy-bromobenzene (Lancaster Synthesis) | | The crude amine was used with no purification. Data for the <i>cis</i> and <i>trans</i> mixture of vinyl nitriles: ¹ H NMR (300MHz, CDCl ₃) δ: 4.25-4.39 (m, 4H), 5.30 and 5.70 (d, 1H), 6.83-7.00 (m, 3H), 7.21-7.40 (m, 1H). |
| 82 | 2-bromoanisole (Lancaster Synthesis) | | ¹ H NMR (MeOD, 400MHz) δ: 1.9 (m, 2H), 2.6 (t, 2H), 2.8 (q, 2H), 3.8 (s, 3H), 6.8 (t, 1H), 6.9 (d, 1H), 7.1 (d, 1H), 7.2 (t, 1H). LRMS: m/z (TS ⁺) 166 (M+H). |
| 83 | 4-bromotoluene (Aldrich Chemical Co.) | | ¹ H NMR (MeOD, 400MHz) δ: 1.9 (m, 2H), 2.2 (s, 3H), 2.6 (t, 2H), 2.8 (t, 2H), 7.0 (s, 4H). LRMS: m/z (TS ⁺) 150 (M+H). |
| 84 | 3-iodobenzylxy-benzene (Aldrich chemical Co.) | | ¹ H NMR (MeOD, 400MHz) δ: 1.8 (bs, 2H), 2.6 (bm, 4H), 5.0 (bs, 2H), 6.9 (d, 3H), 7.1 (m, 2H), 7.3 (m, 3H). LRMS: m/z (TS ⁺) 242 (M+H). |

| Prep | Prec | Y | Analytical Data |
|------|--|---|--|
| 85 | 3-bromoanisole (Lancaster Synthesis) | | ¹ H NMR (CDCl ₃ , 400MHz) δ: 1.7 (m, 2H), 2.6 (t, 2H), 2.7 (t, 2H), 3.8 (d, 3H), 6.3-6.4 (dd, 1H), 6.7 (dd, 1H), 6.9 (d, 1H), 7.1 (m, 1H). LRMS: m/z (TS ⁺) 196 (M+H). |
| 86 | 2,4-dimethoxybromo- benzene (Aldrich Chemical Co.) | | LRMS: m/z (TS ⁺) 196 (M+H). |
| 87 | 5-Bromo-2,2- dimethyl-2,3- dihydrobenzo[b]furan (Preparation 126) | | ¹ H NMR (400MHz, CDCl ₃) δ: 1.40 (s, 6H), 1.70 (tt, 2H), 2.54 (t, 2H), 2.70 (t, 2H), 2.95 (s, 2H), 6.68 (d, 1H), 6.86 (d, 1H), 6.91 (s, 1H). LRMS: M+H, 206. (TS ⁺). |
| 88 | 6-Bromo- tetrahydrobenzopyran (Preparation 125) | | ¹ H NMR (400MHz, CDCl ₃) δ: 1.62-1.78 (m, 2H), 1.84-2.03 (m, 2H), 2.44-2.58 (m, 2H), 2.61-2.78 (m, 4H), 4.03-4.18 (m, 2H), 6.67 (d, 1H), 6.79-6.93 (m, 2H). LRMS: m/z (M+H) 192, ES ⁺ . |
| 89 | 5-bromo-2,2-difluoro- benzodioxolane (Fluorochem) | | ¹ H NMR (400MHz, CDCl ₃) δ: 1.75 (quintet, 2H), 2.60 (t, 2H), 2.67 (t, 2H), 6.80-6.95 (m, 3H). LRMS: M+H, 216. (ES ⁺). |
| 90 | 5-bromo-1-methyl- [1H]-indazole (Preparation 111) | | Used crude with no purification or characterisation. |
| 90a | 5-Bromo-7-methyl- 2,3- dihydrobenzo[b]furan (Preparation 136) | | ¹ H NMR (400MHz, CDCl ₃) δ: 1.9 (m, 2H), 2.1 (s, 3H), 2.55 (t, 2H), 2.85 (t, 2H), 3.10 (t, 2H), 4.45 (t, 2H), 6.70 (s, 1H), 6.80 (s, 1H). LRMS: M+H, 192 (ES ⁺). |
| 91 | 5-Bromo-6-methyl- 2,3- dihydrobenzo[b]furan (Preparation 138) | | ¹ H NMR (400MHz, CDCl ₃) δ: 1.8 (m, 2H), 2.2 (m, 3H), 2.6 (m, 2H), 2.9 (m, 2H), 3.1 (m, 2H), 4.4 (m, 2H), 6.5 (m, 1H), 6.6 (m, 1H). LRMS: M+H, 192 (ES ⁺). |
| 92 | 5-Bromo-2-methyl- 2,3-dihydro-1- benzo[b]furan (Preparation 127) | | ¹ H NMR (400MHz, CDCl ₃) 1.45 (d, 3H), 1.90-2.10 (m, 2H), 2.50-2.63 (m, 2H), 2.88 (dd, 1H), 3.27 (dd, 1H), 4.90 (m, 1H), 6.66 (d, 1H), 6.90 (d, 1H), 6.95 (s, 1H). LRMS: M+H, 192. (ES ⁺). |

PREPARATION 933-(4-Chloro-3-fluorophenyl)-2-propenenitrile

Diethylcyanomethyl phosphonate (3.2ml, 18.9mmol) was taken up in dry THF (20ml) at 0°C under nitrogen, and stirred as a 60% oil dispersion of NaH (756mg, 18.9mmol) was added portionwise over ca. 10min. The resulting grey suspension was then stirred at 0°C for 1h, before a solution of 4-chloro-3-fluoro benzaldehyde (Lancaster Synthesis) (3g, 18.9mmol) in 5ml THF was added dropwise. The whole reaction was then allowed to warm to room temperature over 60h. Water (5ml) was added, and the mixture extracted with EtOAc (3x50ml). The combined organics were dried (MgSO_4) and evaporated to a yellow oil which was purified by column chromatography using 5% EtOAc in pentane as eluant to provide the title product as a mixture of geometric isomers (2.4g, 70%); ^1H NMR (400MHz, CDCl_3) δ : 5.82 (d, 1H), 7.19 (d, 1H), 7.23 (d, 1H), 7.30 (d, 1H), 7.42 (app.t, 1H); LRMS TS⁺ 199.1 ($\text{M}+\text{NH}_4^+$).

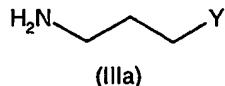
15

PREPARATION 943-(4-Chloro-3-fluorophenyl)-1-propylamine

The vinyl cyanide from Preparation 93 (500mg, 2.75mmol) was taken up in ethanol (36ml) and 0.88 NH_3 solution (18ml) and shaken with 150mg of 30%w/w RaNi under 15psi H_2 pressure overnight. The catalyst was filtered through a short plug of Arbocel and the filtrate was evaporated *in vacuo* and then purified by column chromatography using 90:10:1 (DCM, MeOH, NH_3) as eluant to give the title product (320mg, 62%); ^1H NMR (400MHz, CDCl_3) 1.65-1.78 (m, 2H), 2.53-2.70 (m, 4H), 6.85 (d, 1H), 6.90 (d, 1H), 7.22 (s, 1H); LRMS: m/z (TS⁺) 188 ($\text{M}+\text{H}$).

The following compounds of formula (IIIa), i.e. compounds of general formula III where X is $-(\text{CH}_2)_3-$, were prepared by methods similar to those described in Preparations 93 and 94 from the precursors indicated.

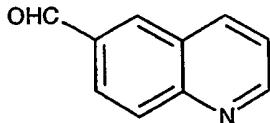
30



| Prep | Prec. aldehyde | Y | Analytical data |
|------|---|---|---|
| 95 | 3-chloro-4-fluoro benzaldehyde (Lancaster Synthesis) | | ¹ HNMR (400MHz, CDCl ₃) δ: 1.62-1.77 (m, 2H), 2.55 (t, 2H), 2.64 (t, 2H), 6.97-6.99 (m, 2H), 7.14 (d, 1H). LRMS: m/z TS ⁺ 188.1 (MH ⁺). |
| 96 | 2,3-difluoro benzaldehyde (Lancaster Synthesis) | | ¹ HNMR (400MHz, CDCl ₃) δ: 1.66-1.78 (m, 2H), 2.58-2.75 (m, 4H), 6.83-6.98 (m, 3H). LRMS: m/z TS ⁺ 343.1 (2MH ⁺). |
| 97 | 2,6-difluoro benzaldehyde (Lancaster Synthesis) | | ¹ HNMR (400MHz, CDCl ₃) δ: 1.68-1.83 (m, 2H), 2.57-2.83 (m, 4H), 6.70-6.92 (m, 2H), 7.01-7.22 (m, 1H). LRMS: m/z TS ⁺ 172.1 (MH ⁺). |
| 98 | 4-trifluoro-methoxy benzaldehyde (Aldrich Chemical Co.) | | ¹ HNMR (400MHz, CDCl ₃) δ: 1.70-1.82 (m, 2H), 2.60 (t, 2H), 2.73 (t, 2H), 7.07 (d, 2H), 7.18 (d, 2H). LRMS: m/z ES ⁺ 220 (MH ⁺). |
| 99 | Preparation 102 | | ¹ HNMR (400MHz, CDCl ₃) δ: 1.66 (m, 2H), 1.89 (m, 2H), 2.42 (m, 2H), 7.36 (m, 1H), 7.50-7.62 (m, 2H), 8.02 (m, 2H), 8.93 (d, 1H). |
| 100 | 4-(methylthio)-benzaldehyde (Aldrich Chemical Co.) | | ¹ HNMR (400MHz, CDCl ₃) δ: 1.68-1.75 (m, 2H), 1.42 (s, 3H), 2.59 (t, 2H), 2.70 (t, 2H), 7.07 (d, 2H), 7.16 (d, 2H). LRMS: M+H, 182. (TS ⁺). |
| 101 | 2,3-dihydrobenzo[b]furan-7-carboxaldehyde (Preparation 128) | | ¹ HNMR (300MHz, CDCl ₃) δ: 1.78 (tt, 2H), 2.64 (t, 2H), 2.73 (t, 2H), 3.22 (t, 2H), 4.55 (t, 2H), 6.78 (dd, 1H), 6.95 (d, 1H), 7.05 (d, 1H). LRMS: M+H, 178. (TS ⁺). |

PREPARATION 102

5 Quinoline-6-carboxaldehyde

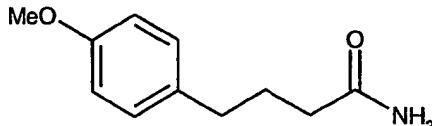


6-Methyl-quinoline (Aldrich Chemical Co.) (1g, 7.0mmol) and selenium dioxide (2.32g, 21.0mmol) were combined in the absence of solvent and heated at 100°C under a nitrogen atmosphere for 16h. The reaction mixture was allowed to cool to room temperature, taken up in MeOH and presorbed onto silica gel. Chromatography using a 3:1 mixture of pentane: EtOAc provided the title product (236mg, 21%); ¹HNMR

(400MHz, CDCl₃) δ: 7.46-7.52 (m, 2H), 7.98 (d, 1H), 8.33-8.37 (m, 2H), 9.03 (d, 1H), 10.18 (s, 1H); m/z (ES⁺) 315 (2MH⁺).

PREPARATION 103

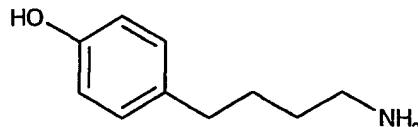
5 4-(4-Methoxyphenyl)-butyramide



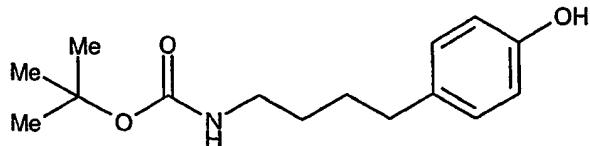
4-(4-Methoxyphenyl)-butyric acid (Aldrich Chemical Co.) (2g, 10.4mmol) was dissolved in 50ml DCM and thionyl chloride (1.85g, 15.5mmol) added dropwise with stirring. After the addition was complete, the mixture was then refluxed for 4h. The solvent was 10 removed *in vacuo*, more was added and then evaporated off and this cycle of addition/evaporation continued until all the thionyl chloride had been removed from the crude mixture. This mixture was dissolved in 20ml DCM and added dropwise to a stirred solution of 0.88NH₃ at 0°C. After the addition was complete, the whole was stirred for 4h, the organic layer separated, dried (Na₂CO₃) and evaporated to give the title product 15 as a white solid of the amide (1.5g), which was used with no further purification.

PREPARATION 104

4-(4-Hydroxyphenyl)-butyramine



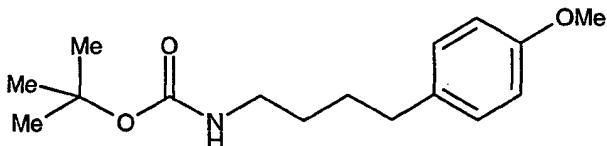
20 The product from Preparation 103 (38g, 0.20moles) was added portionwise to a stirred solution of LiAlH₄ (15g, 0.40moles) in 1L of THF, and the whole then refluxed for 16h. The excess hydride was destroyed by addition of EtOAc (400ml), and most of the solvents were then removed under reduced pressure. Addition of 30ml of 2N NaOH solution (CAUTION!) completed the decomposition of the hydride, and the resulting 25 solution was then acidified with 1N HCl and taken up by extraction into water (2x200ml). Basification of the aqueous extracts with 2N NaOH, extraction with EtOAc, drying (MgSO₄) and evaporation led to a yellow oil of crude amine. This oil was refluxed in 160ml aqueous HBr for 4h, and was then poured onto 100ml water. Solid Na₂CO₃ was then added until a pH of 9-10 was obtained. The mixture was thoroughly extracted with 30 DCM (3x100ml), dried (MgSO₄) and evaporated to a white solid which was recrystallised from benzene to give the title product (6.4g, 35%); m.p. 114-116°C.

PREPARATION 105Tert-Butyl-4-(4-hydroxyphenyl)butylcarbamate

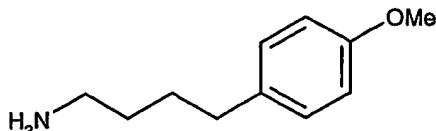
5 Di-*tert*-butyl dicarbonate (1.06g, 4.8mmol) was added in one portion to a stirred solution of the product from Preparation 104 (400mg, 2.4mmol) in a mixture of water (10ml) and dioxan (10ml) under nitrogen. The reaction was stirred for 72h, after which time potassium carbonate (2.0g, 14.4mmol) was added in one portion and the mixture stirred for a further 23h to completely hydrolyse any ester formed during the reaction. The

10 mixture was transferred to a separating funnel, and the organic layer separated, dried over MgSO₄ and evaporated to a yellow oil. The oil was chromatographed using a 2:1 mixture of pentane:EtOAc as eluant to give the title product (555mg, 86%); ¹HNMR (400MHz, CDCl₃) δ: 1.41-1.62 (m, 13H), 2.53 (t, 2H), 3.12 (m, 2H), 4.48 (1H, brs), 4.80 (s, 1H), 6.74 (d, 2H), 7.01 (d, 2H).

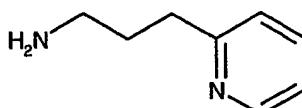
15

PREPARATION 106Tert-Butyl-(4-4-methoxyphenyl)butylcarbamate

A 60% dispersion of NaH in mineral oil (88mg, 2.2mmol) was added to a stirred solution of the product from Preparation 105 (555mg, 2.1mmol) in THF (7ml) at room temperature under nitrogen. The mixture was stirred for 15min, before adding MeI (0.14ml, 2.2mmol) in one portion and stirring at room temperature for a further 16h. The reaction was diluted with EtOAc (20ml) and washed with 3% NaHCO₃ solution (15ml). The organic layer was dried over MgSO₄ and purified by chromatography using DCM as eluant to provide the title compound (500mg, 85%); ¹HNMR (400MHz, CDCl₃) δ: 1.40-1.63 (m, 13H), 2.57 (t, 2H), 3.13 (m, 2H), 3.78 (s, 3H), 4.46 (1H, brs), 6.82 (d, 2H), 7.06 (d, 2H).

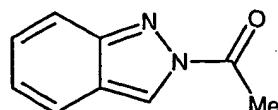
PREPARATION 1074-(4-Methoxyphenyl)butylamine

The product from Preparation 106 (500mg, 1.8mmol) was taken up in 3ml of DCM and 5 3ml of TFA, and stirred under nitrogen for 16h. The mixture was then poured onto 50ml of a 10% aqueous solution of Na_2CO_3 and the organics extracted with EtOAc (2x50ml). The combined organic layers were dried (MgSO_4) and evaporated to provide the title product (300mg, 94%), which was used with no further purification.

10 PREPARATION 1083-(2-pyridinyl)-1-propanamine

2-Vinyl pyridine (105g) and acetic anhydride (204g) were combined at room temperature, and a solution of KCN (130g) in 250ml of water was added dropwise to the 15 stirring solution. The rate of addition was adjusted to maintain a gentle reflux. After the addition was complete, the mixture was refluxed for 22h, and the pH of the solution then adjusted to 8 with aqueous Na_2CO_3 solution. The mixture was extracted with DCM (600ml), the extracts dried over MgSO_4 and then evaporated to a brown oil. The oil was then vacuum distilled at approximately 0.6mmHg pressure. The product distilled over as 20 a clear oil at 100-107°C in 56% yield. The oil of 2-(2-cyanoethyl)-pyridine (200mg, 1.5mmol) was taken up in 6ml of EtOH and treated with 2ml of 0.88 NH_3 solution and 50mg of RaNi. The mixture was hydrogenated at 30psi H_2 pressure for 16h, and was then filtered and evaporated to give the title product (ca. 200mg) which was used with no further purification.

25

PREPARATION 1092-Acetyl-2H-indazole

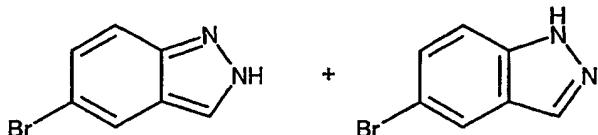
Indazole (3.5g, 29.6mmol) and acetic anhydride (35ml) were heated at 60°C under 30 nitrogen for 3h. Excess acetic anhydride was evaporated and the remaining oily residue

partitioned between 3% aqueous NaHCO₃ (20ml) and EtOAc (30ml). The organic layer was separated, dried (MgSO₄) and evaporated to provide the title product (4.5g, 96%); ¹HNMR (400MHz, CDCl₃) δ: 2.80 (s, 3H), 7.37 (t, 1H), 7.58 (t, 1H), 7.75 (d, 1H), 8.46 (d, 1H).

5

PREPARATION 110

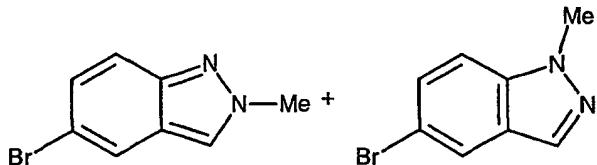
5-Bromo-2H-indazole and 5-bromo-1H-indazole



The product from Preparation 109 (450mg, 2.8mmol) was taken up in acetic acid (0.5ml) 10 and stirred at room temperature under nitrogen. Bromine (0.5ml) was added over about 1min, and the reaction then stirred for a further 16h. Excess bromine was removed by bubbling nitrogen gas through the solution for 30min, whereupon a thick solid was produced in the flask. 5ml of toluene was added, and the whole evaporated *in vacuo* and the residue triturated with pentane (5ml). The remaining solid was filtered off and 15 dried under vacuum before treating with 6ml each of 1M NaOH and EtOH. The mixture was heated to 50°C for 1h and then allowed to cool to room temperature. The EtOH was evaporated, and the residue extracted with DCM (2x10ml), which was then dried (MgSO₄) and evaporated to give 400mg of a 3:1 inseparable mixture of the title 1-H:2-H indazole isomers; ¹HNMR (400MHz, CDCl₃) δ: 7.41 (d, 1H), 7.49 (d, 1H), 7.92 (s, 1H), 20 8.02 (s, 1H).

PREPARATION 111

2-Methyl-5-bromo-2H-indazole and 1-Methyl-5-bromo-1H-indazole



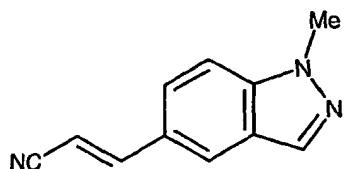
25 The mixture of isomers from Preparation 110 (400mg, 2.0mmol) was taken up in MeOH (8ml) at room temperature under nitrogen and NaOMe (223mg, 4.0mmol) added in one portion. MeI (0.32ml, 5mmol) was added dropwise and the mixture heated at reflux for 4h. The reaction was allowed to cool to room temperature and then concentrated to low volume (ca. 3ml) before partitioning between EtOAc (20ml) and 3% aqueous NaHCO₃ 30 solution. The organic layer was separated, dried (MgSO₄) and purified by chromatography using 99:1 DCM:MeOH as eluant to provide the 1-Me isomer (100mg,

23%) and the 2-Me isomer and (112mg, 26%); 1-Methyl isomer; ^1H NMR (400MHz, CDCl_3) δ : 4.08 (s, 3H), 7.30-7.50 (m, 2H), 7.82 (s, 1H), 7.92 (s, 1H); 2-Methyl isomer; ^1H NMR (400MHz, CDCl_3) δ : 4.13 (s, 3H), 7.35 (d, 1H), 7.59 (d, 1H), 7.81 (s, 1H), 7.85 (s, 1H).

5

PREPARATION 112

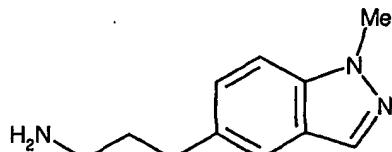
3-(1-Methyl-1*H*-indazol-5-yl)-2-propenenitrile



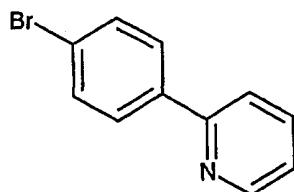
The 1-methyl isomer from Preparation 111 (100mg, 0.47mmol) was taken up in dioxan (6ml), and potassium carbonate (72mg, 0.52mmol), acrylonitrile (0.035ml, 0.52mmol), $\text{Pd}_2(\text{dba})_3$ (43mg, 0.047mmol) and $\text{P}t\text{er}t\text{Bu}_3$ (0.038ml, 0.16mmol) were added in sequence. The reaction was then refluxed for 3h under a nitrogen atmosphere before cooling to room temperature, filtering through a short plug of arbocel and evaporation of the filtrate *in vacuo*. The residue was then chromatographed using 99:1 DCM:MeOH to give the title product (57mg, 66%) as a mixture of *cis* and *trans* geometric isomers; ^1H NMR (300MHz, CDCl_3) δ : 4.11 (s, 3H), 5.40 and 5.84 (d, 1H), 7.37-8.18 (m, 5H).

PREPARATION 113

3-(1-Methyl-1*H*-indazol-5-yl)-1-propanamine



The product from Preparation 112 (55mg, 0.29mmol) was taken up in ethanol (4ml) and 0.88NH₃ solution (1ml) and subjected to hydrogenation at 30psi and room temperature under 10mg of 30%w/w RaNi for 2h. The mixture was filtered through a short plug of Arbocel and the filtrate evaporated to give the title product which was used with no further purification.

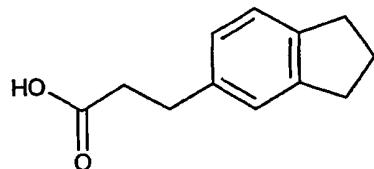
PREPARATION 1142-(4-Bromophenyl)-pyridine

⁷BuLi (1.6M in hexanes, 34.4mls, 55mmol) was added dropwise to a stirred solution of

5 1,4-dibromobenzene (11.8g, 50mmol) in 100ml of dry THF at -60°C. The mixture was stirred for 15min at this temperature before a solution of ZnCl₂ (0.5M in THF, 100ml, 50mmol) in THF was added dropwise. The mixture was allowed to warm to room temperature over 90min, and then Pd(PPh₃)₄ (200mg) was added, followed immediately by 2-bromopyridine (4.8ml, 50mmol). The whole was stirred at room temperature

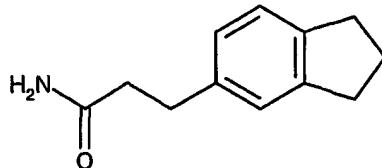
10 overnight, then evaporated to low (10ml) volume and diluted with EtOAc (400ml). The solution was washed with a solution of 32g of EDTA in 200ml water and brine (200ml), dried (MgSO₄) and evaporated to a yellow/green solid. This solid was purified by column chromatography using 1:1 hexane:DCM as eluant to provide the title product (8.3g, 71%); m/z MH⁺ 234 (TS⁺); Found C 56.61%, H 3.37%, N 5.90%; Calcd. C 56.44%, H 3.44%, N 5.98%.

15

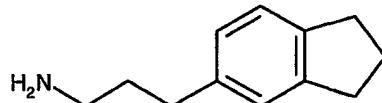
PREPARATION 1153-(2,3-Dihydro-1H-inden-5-yl)-propanoic acid

20 3-(2,3-Dihydro-1H-inden-5-yl)-propanoic acid (500mg, 2.66mmol) (available from Aldrich) was taken up in ethanol (40ml) and hydrogenated at 15psi H₂ pressure with 40mg of 10% Pd/C for 4h. The mixture was filtered through a short plug of Arbocel and the filtrate evaporated to give the title product (560mg, approx. quantitative) which was used with no further purification; ¹HNMR (400MHz, CDCl₃) δ: 1.98-2.07 (m, 2H), 2.75 (t, 2H), 2.80-2.90 (m, 6H), 6.95 (d, 1H), 7.03 (s, 1H), 7.08 (d, 1H); LRMS: m/z ES⁻ 189 (M-H).

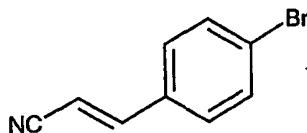
25

PREPARATION 1163-(2,3-Dihydro-1H-inden-5-yl)-propanamide

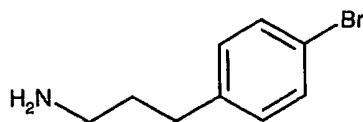
The product from preparation 115 (190mg, 1mmol) was dissolved in DCM (2ml) at room temperature under nitrogen, and firstly 132 μ l (1.5mmol) of oxalyl chloride, and then 1 drop of DMF were added. After the effervescence had subsided, the mixture was stirred at room temperature for 3h and then concentrated *in vacuo*. The residue was redissolved in 2ml of THF and 0.6ml of 0.88NH₃ solution added, and the whole stirred for 4 days. The reaction was quenched with water and extracted into EtOAc (2x10ml). The combined organics were dried (MgSO₄) and evaporated to give the title product (190mg, 99%); ¹HNMR (400MHz, CDCl₃) δ : 1.96-2.05 (m, 2H), 2.49 (t, 2H), 2.81-2.92 (m, 6H), 5.32 (brs, 2H), 6.93 (d, 1H), 7.05 (s, 1H), 7.08 (d, 1H); LRMS: m/z (ES⁻) 189 (M-H).

PREPARATION 11715 3-(2,3-Dihydro-1H-inden-5-yl)-propylamine

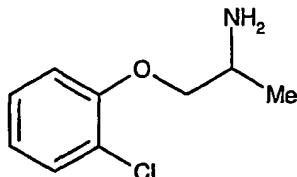
The amide from Preparation 116 (170mg, 0.9mmol) was dissolved in dry THF (3ml) at 0°C under nitrogen and stirred as a solution of LiAlH₄ in THF (1M, 0.9ml, 0.9mmol) was added dropwise with considerable effervescence. The reaction was warmed to 60°C and stirred at this temperature overnight. The mixture was quenched with water (1ml), 1N NaOH solution was added (1ml) and the solution extracted with EtOAc (2x50ml), dried (MgSO₄), filtered and concentrated to a pale yellow oil. This oil was purified by column chromatography using 90:10:1 (DCM, MeOH, NH₃) as eluant to give the title product (30mg, 35%); ¹HNMR (400MHz, CDCl₃) δ : 1.72-1.77 (m, 2H), 1.96-2.03 (m, 4H), 2.57 (t, 2H), 2.70 (t, 2H), 2.80-2.85 (m, 4H), 6.90 (d, 1H), 7.02 (s, 1H), 7.09 (d, 1H); LRMS: m/z (TS⁺) 176 (M+H).

PREPARATION 1183-(4-Bromophenyl)-2-propenenitrile

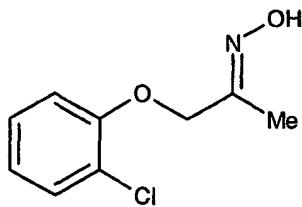
A 60% suspension of NaH in mineral oil (2.16g, 54.1mmol) was suspended in THF (50ml) and cooled to 0°C under nitrogen. Diethyl-cyanomethyl phosphonate (8.74ml, 54.1mmol) was added dropwise and the whole stirred at 0°C for 30min. 4-bromobenzaldehyde (10g, 54.1mmol) was then added dropwise as a solution in 20ml THF, and the mixture allowed to warm to room temperature overnight. The reaction was quenched with water, extracted with EtOAc (3x50ml), dried (MgSO_4) and then filtered and evaporated to a yellow oil. This oil was taken up in a 9:1 mixture of pentane:EtOAc from which the title product crystallised (5.8g, 52%); ^1H NMR (400MHz, CDCl_3) δ : 5.82 (d, 1H), 7.21-7.28 (m, 3H), 7.50 (d, 2H).

PREPARATION 11915 3-(4-Bromophenyl)-1-propanamine

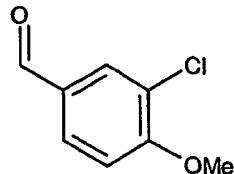
The title compound was prepared by a modified procedure of that described by Iddon *et al.* (*J.C.S. Perkin I*, 1977, 2357). Solid LiAlH_4 (1.2g, 31.6mmol) was suspended in diethyl ether (35ml) and stirred under nitrogen as the suspension was heated to *ca.* 50°C. A solution of the vinyl cyanide from Preparation 118 (2.06g, 9.88mmol) was added dropwise as a solution in ether (20ml) and the mixture then heated for 90min. After this time, the heating was stopped, and the reaction was stirred at room temperature for 16h. Water was added, followed by 1N NaOH (30ml) and EtOAc (60ml) and the whole stirred vigorously for 30min. The organic layer was separated, dried (MgSO_4) and evaporated to a yellow oil which was purified by column chromatography using 90:10:1 (DCM, MeOH, NH_3) as eluant to provide the title product (740mg, 35%); ^1H NMR (400MHz, CDCl_3) δ : 1.65-1.74 (m, 2H), 2.52 (t, 2H), 2.66 (t, 2H), 7.02 (d, 2H), 7.35 (d, 2H); LRMS: m/z (TS⁺) 214 (M+H).

PREPARATION 1201-(2-Chlorophenoxy)-2-propanamine

The product from preparation 121 (11g, 55.2mmol) in diethyl ether (41ml) was added dropwise to a suspension of lithium aluminium hydride (4.1g, 108mmol) in diethyl ether (110ml) under nitrogen. The reaction mixture was refluxed for 4 hours before the addition of ethyl acetate then water. The aqueous layer was acidified with 4N hydrochloric acid shaken and then separated before been made alkaline with 40% sodium hydroxide solution. The aqueous layer was then extracted with diethyl ether (3x100ml) and the combined organic extracts were dried over magnesium sulphate. The diethyl ether extracts were acidified with hydrogen chloride and the resulting precipitate filtered. The solid was recrystallised from ethanol/petroleum ether (b.p. 60-80 degC) to give the title product (2.5g, 20%), m.p. 126-127°C; ¹H NMR (CDCl₃ 400MHz) δ: 1.55 (d, 3H), 3.80 (q, 1H), 4.20 (d, 2H), 6.90-7.00 (m, 2H), 7.15 (t, 1H), 7.30 (d, 1H), 8.60 (bs, 3H); Anal. Found C, 48.9; H, 6.0; N, 6.5. C₉H₁₃NOCl₂ requires C, 48.7; H, 5.9; N, 6.3%.

PREPARATION 1211-(2-Chlorophenoxy)-2-propanone oxime

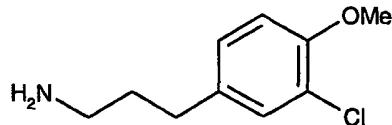
1-(2-Chlorophenoxy)acetone (106.6g, 0.58mol) (*J. Am. Chem. Soc.*, 75, 1953, 1134) was added to a solution of hydroxylamine hydrochloride (27.8g, 4mol) in 2N sodium hydroxide solution (420ml) and sufficient ethanol to give a clear solution. The reaction mixture was refluxed for 30 minutes then concentrated *in vacuo*, the crude residue was extracted with diethyl ether (3x200ml). The combined organic layers were dried over magnesium sulphate and concentrated *in vacuo*. The residue was distilled to give the title product (134-136°C/1.35mmHg) (4.5g, 3.9%); ¹H NMR (CDCl₃ 400MHz) δ: 2.05 (s, 3H), 5.00 (s, 2H), 6.90-7.00 (m, 2H), 7.10 (t, 1H), 7.30 (d, 1H), 7.60 (s, 1H); Anal. Found C, 54.95; H, 5.05. C₉H₁₀NO₂Cl requires C, 54.15; H, 5.05%.

PREPARATION 1223-(4-Methoxy-3-chlorophenyl)-1-propylamine

5 4-Methoxy-benzaldehyde (Aldrich) (42g, 0.31mole) and pyridine (0.6ml, catalytic) were stirred together under nitrogen and sulfonyl chloride (51g, 0.37mole) added over 30min, maintaining the internal temperature of the reaction at between 25 and 30°C. There was a vigorous evolution of gas. The mixture was stirred at room temperature for a further 30min, and then warmed to 70°C for 4h. Excess reagents were removed by evaporation

10 *in vacuo* and the residue taken up in 50ml diisopropyl ether and poured onto 500ml hexane with vigorous stirring, from which the product precipitates. The solid was filtered off and washed with hexane and then dried *in vacuo* to give the title product (40.3g, 77%), m.p. 55-56°C; ¹HNMR (400MHz, CDCl₃) δ: 3.99 (s, 3H), 7.05 (dd, 1H), 7.91 (d, 1H), 9.86 (s, 1H); Anal. Found: C, 56.13; H, 4.14%. C₈H₇ClO₂ requires C, 56.33; H, 4.14%.

15 4.14%.

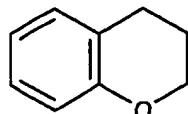
PREPARATION 1233-(4-Methoxy-3-chlorophenyl)-1-propylamine

20

The product from Preparation 122 was converted to a diastereomeric mixture of the corresponding vinyl nitriles according to Preparation 93. This mixture (300mg, 1.55mmol) was taken up in DCM (6ml) at room temperature under nitrogen and *tetra*-n-butyl-ammonium borohydride (1.6g, 6.2mmol) added portionwise over 5min. The mixture was then refluxed for 4h and then evaporated to dryness. The residue was taken up in approx. 6ml of 10% HCl (aq.) and then refluxed for a further 1h. The reaction was cooled, extracted with EtOAc (3x30ml), dried (MgSO₄) and evaporated to a yellow oil. This oil was columned in 95/5/0.5, then 95/5/1 DCM/MeOH/NH₃ to give the title product (75mg, 24%); ¹HNMR (400MHz, CDCl₃) δ: 1.60-1.74 (m, 2H), 2.56 (t, 2H), 2.67 (t, 2H), 3.82 (s, 3H), 6.79 (d, 1H), 6.98 (d, 1H), 7.15 (s, 1H).

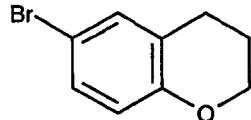
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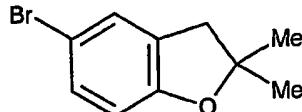
PREPARATION 124Chroman

5 4-Chromanol (Aldrich) (2.77g, 18.4mmol) was taken up in acetic anhydride (3.5ml, 36.9mmol) and acetic acid (30ml) and refluxed for 3h, and then allowed to cool to room temperature over 16h. 10% w/w Pd/C was then added to the solution and the whole hydrogenated at 40p.s.i. hydrogen pressure for 16h. The catalyst was filtered through a pad of Arbocel and the filtrate evaporated to low (5ml) volume. The remaining liquid was
10 dissolved in EtOAc (30ml) and washed with water, then NaHCO₃ solution (100ml of each). The organic layer was dried over MgSO₄ and evaporated to a pale yellow oil. This oil was columned in 10% EtOAc/pentane to give the title product (2.1g, 85%);
15 ¹HNMR (400MHz, CDCl₃) δ: 1.93-2.04 (m, 2H), 2.79 (t, 2H), 4.18 (t, 2H), 6.78-6.83 (m, 2H), 7.00-7.10 (m, 2H).

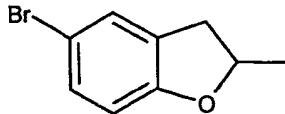
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PREPARATION 1256-Bromochroman

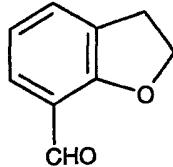
20 The product from Preparation 124 (1g, 7.5mmol) was taken up in DCM (10ml) and bromine (403μl, 7.8mmol) was added as a solution in DCM (3ml) over several minutes. Towards the end of the addition, a brown colour persisted in the solution. The mixture was stirred at room temperature for 3h and then washed with water (20ml) and brine (20ml) and the organic layer separated, dried (MgSO₄) and evaporated to a thick yellow oil, which was purified by column chromatography using 5% EtOAc in pentane to give
25 the title product (1.3g, 82%); ¹HNMR (400MHz, CDCl₃) δ: 1.90-1.98 (m, 2H), 2.73 (t, 2H), 4.14 (t, 2H), 6.61 (d, 1H), 7.08-7.15 (m, 2H).

PREPARATION 1265-Bromo-2,2-dimethyl-2,3-dihydrobenzo[b]furan

2,2-Dimethyl-2,3-dihydrobenzo[b]furan (prepared according to the method of Baker and Shulgin, *J. Org. Chem.*, **28**, 1963, 2468) (500mg, 3.38mmol) was taken up in dichloroethane (5.5ml) and stirred at room temperature under nitrogen, and N-bromosuccinimide (661mg, 3.72mmol) added in one portion. The reaction was then refluxed for 2h, ether was added (10ml) and a white precipitate of succinimide filtered off. The filtrate was evaporated to dryness, and then purified by column chromatography using 5% ether in pentane as eluant to give the title product (604mg, 79%); ¹HNMR (400MHz, CDCl₃) δ: 1.43 (s, 6H), 2.92 (s, 2H), 6.54 (d, 1H), 7.16 (d, 1H), 7.19 (s, 1H); LRMS: M+H, 227. (TS⁺).

PREPARATION 1275-Bromo-2-methyl-2,3-dihydro-1-benzof[b]furan

The title product was prepared from 2-methyl-2,3-dihydro-1-benzof[b]furan (commercially available from TCI, Japan) using an identical procedure to that used for Preparation 126 (87%); ¹HNMR (400MHz, CDCl₃) δ: 1.43 (d, 3H), 2.80 (dd, 1H), 3.29 (dd, 1H), 4.94 (m, 1H), 6.61 (d, 1H), 7.18 (d, 1H), 7.22 (s, 1H).

PREPARATION 1282,3-Dihydrobenzo[b]furan-7-carboxaldehyde

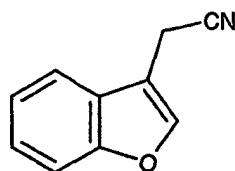
2,3-Dihydrobenzo[b]furan (Maybridge Chemicals) (25g, 0.21mole) was taken up in DCM (500 ml) and stirred under nitrogen at 0°C. SnCl₄ (36.5ml, 0.3mole) was added in one portion to produce a pale yellow solution. Dichloromethyl methyl ether (18.8ml, 0.21mole) was then added and the solution stirred for 30min, after which time the cooling bath was removed and the reaction poured onto ice-water (1000 ml). The

organic layer was separated, washed with water (2x100ml), 2N HCl (100ml) and brine (50ml), and then charcoal (30g) and Na_2SO_4 were added to the solution. Filtration through Celite and evaporation gave a black oil, which was subjected to flash chromatography using 7-10% EtOAc in pentane to give the title product (190mg, 0.01%);

5 $^1\text{HNMR}$ (400MHz, CDCl_3) δ : 3.24 (t, 2H), 4.75 (t, 2H), 6.93 (t, 1H), 7.40 (d, 1H), 7.59 (d, 1H), 10.2 (s, 1H); LRMS: (M+H) 149, TS^+ . Anal. Found: C, 72.98; H, 5.46%. $\text{C}_9\text{H}_8\text{O}_2$ requires C, 72.96; H, 5.44%.

PREPARATION 129

10 1-Benzofuran-3-ylacetonitrile



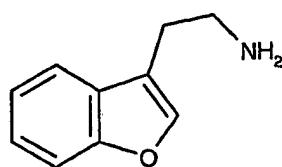
Sodium hydride (268mg, 6.7mmol) was slurried in dry THF (10ml) at 0°C under nitrogen and diethyl cyanomethyl phosphonate (1.1ml, 6.7mmol) added dropwise and the whole stirred for 45min. 3-Coumaranone (Lancaster) (900mg, 6.7mmol) was then added

15 dropwise and the whole stirred at room temperature for 45min. The reaction was diluted with EtOAc (15ml) and water (15ml), and the organic layer was then separated, dried (MgSO_4) and evaporated and the residue flash chromatographed using 0-5% EtOAc in pentane to give the title product (940mg, 91%); $^1\text{HNMR}$ (400MHz, CDCl_3) δ : 3.77 (s, 2H), 7.25-7.40 (m, 2H), 7.52 (dd, 1H), 7.58 (dd, 1H), 7.67 (s, 1H); LRMS: M+ NH_4^+ , 175. TS^+ .

20

PREPARATION 130

2-(1-Benzofuran-3-yl)-ethylamine

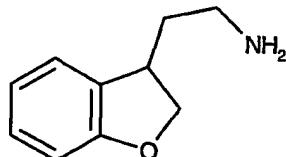


25 The product from Preparation 129 (400mg, 2.55mmol) was combined with ammonium hydroxide solution (10ml), ethanol (20ml) and 30wt% Ra-Ni (120mg, cat.) and hydrogenated at 30p.s.i. hydrogen pressure at room temperature for 16h. The catalyst was filtered through a plug of Arbocel and the yellow-brown filtrate chromatographed using 0-5% MeOH in DCM to provide the title product (380mg, 93%); $^1\text{HNMR}$ (400MHz,

CDCl_3 δ : 1.20 (brs., 2H), 2.80 (t, 2H), 3.02 (t, 2H), 7.15-7.25 (m, 2H), 7.43 (dd, 2H), 7.55 (dd, 1H); LRMS: $M+\text{H}$, 162. (ES^+).

PREPARATION 131

5 2-(2,3-Dihydro-1-benzofuran-3-yl)-ethylamine

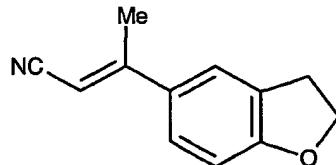


The product from Preparation 130 (200mg, 1.24mmol) was mixed with ethanol (20ml) and 20mg of 10wt% Pd/C and hydrogenated at 40p.s.i. hydrogen pressure for 48h. A further 20mg of catalyst was added, and the whole hydrogenated at 60p.s.i. and 40°C for a further 72h. The catalyst was filtered through a short plug of Arbocel, and the filtrate evaporated to dryness. The residue was purified by column chromatography using 90/10/1 DCM/MeOH/ NH_3 as eluant to provide the title product (11mg, 55%);

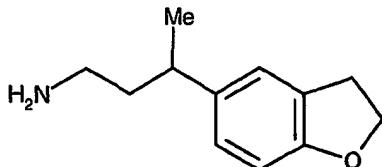
10 $^1\text{H}\text{NMR}$ (400MHz, CDCl_3) δ : 1.81 (m, 1H), 1.98 (m, 1H), 2.75-2.83 (m, 2H), 3.50 (m, 1H), 4.22 (t, 1H), 4.60 (t, 1H), 6.72 (d, 1H), 6.85 (t, 1H), 7.10 (t, 1H), 7.20 (d, 1H); LRMS: 15 $M+\text{H}$, 164. (ES^+).

PREPARATION 132

(2E and 2Z)-3-(2,3-Dihydro-1-benzofuran-5-yl)-2-butenenitrile

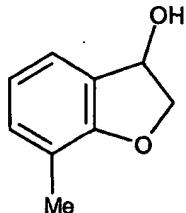


20 To a stirred suspension of sodium hydride (247mg, 6.16mmol) in dry THF (6ml) at 0°C under nitrogen was added a solution of diethylcyanomethyl phosphonate (0.98ml, 6.16mmol) in 2ml THF and the whole stirred at 0°C for 1h. 5-Acetyl-2,3-dihydro[b]benzofuran (Aldrich) (1g, 6.16mmol) in THF (2ml) was added dropwise and the whole stirred at room temperature for 16h. Water (20ml) and EtOAc (20ml) were added, 25 the organic layer separated, and the aqueous layer extracted with EtOAc (2x20ml). The combined organics were dried over MgSO_4 , filtered and evaporated to afford a pale brown oil which solidified on standing. This solid was purified by column chromatography using 20-30% EtOAc in pentane as eluant to give the title product (789mg, 69%); $^1\text{H}\text{NMR}$ (400MHz, CDCl_3) δ : 2.4 (s, 3H), 3.2 (t, 2H), 4.6 (t, 2H), 5.5 (s, 1H), 6.7 (d, 1H), 7.2 (d, 1H), 7.3 (s, 1H); LRMS: $M+\text{NH}_4$ 203 (ES^+).

PREPARATION 1333-(2,3-Dihydro-1-benzofuran-5-yl)-butylamine

5 The product from Preparation 132 was dissolved in ethanol (20ml) and ammonium hydroxide solution (5ml), and the whole hydrogenated at 30p.s.i. hydrogen pressure over 200mg of 30wt% Ra-Ni for 16h. A further 100mg of catalyst was then added and the hydrogenation continued for a further 16h. The reaction mixture was filtered through a short plug of Arbocel, and the filtrate evaporated *in vacuo* to low volume. The residue

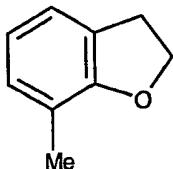
10 was then co-evaporated from toluene (2x20ml) to remove last traces of water to provide the title product (780mg, 96%), which was used with no further purification; ^1H NMR (400MHz, CDCl_3) δ : 1.2 (d, 3H), 1.7 (q, 2H), 2.5 (m, 2H), 2.65 (m, 1H), 3.1 (t, 2H), 4.45 (t, 2H), 6.6 (d, 1H), 6.9 (d, 1H), 7.0 (s, 1H); LRMS: M+H 192. (ES $^+$).

15 PREPARATION 1347-Methyl-2,3-dihydro-1-benzofuran-3-ol

To a stirred suspension of trimethyl sulfoxonium chloride (3.78g, 0.03mole) in dry THF (60ml) was added sodium hydride (1.16g, 0.03mole) and the whole warmed to reflux for

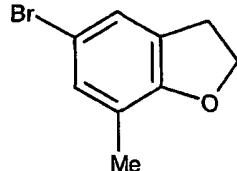
20 1h. 2-Hydroxy-3-methyl-benzaldehyde (Lancaster) (4g, 0.03mole) was added in 30ml THF *via* syringe and the resulting orange suspension stirred at reflux for 5h. Water (50ml) was added, and the organics were extracted with ether (3x50ml). The combined organics were dried (MgSO_4), filtered and evaporated *in vacuo* to an orange oil which was purified by column chromatography using 15-25% EtOAc in pentane to give the title

25 product (2g, 45%); ^1H NMR (400MHz, CDCl_3) δ : 2.2 (s, 3H), 4.45 (m, 2H), 5.3 (m, 1H), 6.8 (t, 1H), 7.1 (d, 1H), 7.2 (d, 1H); LRMS: M+H, 151. (ES $^+$).

PREPARATION 1357-Methyl-2,3-Dihydro-1-benzofuran

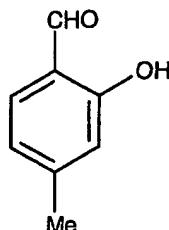
To a stirred solution of the product from Preparation 134 (500mg, 3.3mmol) in acetic acid (5ml) was added acetic anhydride (0.63ml, 6.7mmol) and the whole stirred at reflux under nitrogen for 2h, then allowed to warm to room temperature over 16h. 10wt% Pd/C (30mg) was added directly to the solution and hydrogenated at 40p.s.i. hydrogen pressure for 16h at room temperature. The catalyst was filtered through a plug of Arbocel and the filtrate concentrated *in vacuo* to a pale yellow residue, which was dissolved in EtOAc (20ml), washed with water (3x20ml), NaHCO₃ (20ml), dried (MgSO₄) and evaporated to a pale yellow oil. This oil was purified by column chromatography using 3% EtOAc in pentane as eluant to provide the title product (261mg, 58%); ¹HNMR (400MHz, CDCl₃) δ: 2.2 (s, 3H), 3.2 (t, 2H), 4.55 (t, 2H), 6.75 (t, 1H), 6.9 (d, 1H), 7.05 (d, 1H).

15

PREPARATION 1365-Bromo-7-methyl-2,3-dihydro-1-benzofuran

To a stirred solution of the product from Preparation 135 (200mg, 1.49mmol) in dichloroethane (2.5ml) was added *N*-bromosuccinimide (318mg, 1.79mmol) and the whole stirred at reflux for 16h under nitrogen. The mixture was concentrated *in vacuo* to afford a pale orange-brown solid which was purified by column chromatography using 1% EtOAc in pentane as eluant to afford the title product (112mg, 35%); ¹HNMR (400MHz, CDCl₃) δ: 2.1 (s, 3H), 3.15 (t, 2H), 4.5 (t, 2H), 7.0 (s, 1H), 7.1 (s, 1H).

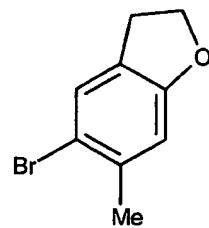
25

PREPARATION 1372-Hydroxy-4-methyl-benzaldehyde

To a stirred solution of 3-methyl-phenol (1g, 9.2mmol) in toluene (5ml) at room temperature under nitrogen was added SnCl_4 (241mg, 0.92mmol) and *tri-n*butylamine (0.6ml, 2.77mmol). After 20min, paraformaldehyde (611mg, 20.3mmol) was added and the whole stirred at 100°C for 16h. The reaction mixture was diluted with water (20ml) and acidified with 2N HCl to pH2. The solution was extracted with ether (25ml), washed with brine (20ml), dried (MgSO_4) filtered and evaporated to a brown oil. This oil was purified by column chromatography using 5% EtOAc in pentane as eluant to provide the title product (319mg, 25%); ^1H NMR (400MHz, CDCl_3) δ : 2.3 (s, 3H), 6.75 (m, 2H), 7.35 (d, 1H), 9.75 (s, 1H), 11.00 (s, 1H).

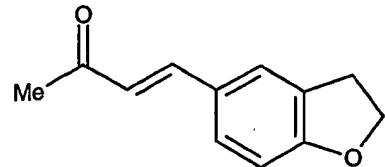
PREPARATION 138

15 5-Bromo-6-methyl-2,3-dihydrobenzofuran



The product from Preparation 137 was taken through to the title compound by an identical 3-step sequence as detailed in Preparations 134-136; ^1H NMR (400MHz, CDCl_3) δ : 2.3 (s, 3H), 3.55 (t, 2H), 4.5 (t, 2H), 6.7 (s, 1H), 7.3 (s, 1H); LRMS: M+H, 214. (ES^+).

20

PREPARATION 139(3E)-4-(2,3-Dihydro-1-benzofuran-5-yl)-3-buten-2-one

2,3-Dihydrobenzo[b]furan-5-carboxaldehyde (Aldrich Chemicals) (2g, 13.5mmol),

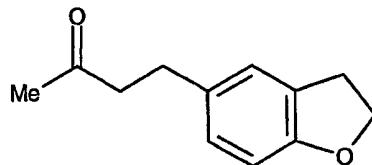
25 acetone (2.73ml, 37.1mmol), water (1.35ml) and 10% NaOH (aq.) (0.34ml) were added

together and the whole stirred at room temperature for 16h. The yellow solid was redissolved in approx. 15ml DCM and 2N HCl added to achieve a solution of pH2. Water (10ml) was added and the organic layer was extracted with DCM (2x20ml). The aqueous layers were separated, and re-extracted with DCM (2x15ml). The combined 5 organics were dried (MgSO_4) and concentrated *in vacuo* to a yellow solid which was purified by column chromatography using 15-30% EtOAc in pentane as eluant to provide the title product (2.13g, 84%); ^1H NMR (400MHz, CDCl_3) δ : 2.3 (s, 3H), 3.2 (t, 2H), 4.6 (t, 2H), 6.5 (d, 1H), 6.75 (d, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.45 (d, 1H); LRMS: $\text{M}+\text{H}$, 189. (ES^+).

10

PREPARATION 140

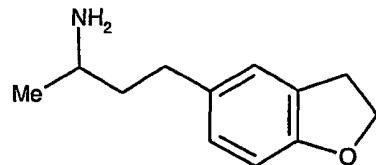
4-(2,3-Dihydro-1-benzofuran-5-yl)-2-butanone



The product from Preparation 139 (2.12g, 11.3mmol) was taken up in ethanol (40ml) 15 and hydrogenated at 15p.s.i. hydrogen pressure over 200mg 10wt% Pd/C for 4h. The mixture was filtered through a short plug of Arbocel and the filtrate evaporated *in vacuo* to a colourless oil which was purified by column chromatography using 15-25% EtOAc in pentane to provide the title product (1.53g, 71%); ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 2.7 (t, 2H), 2.8 (t, 2H), 3.1 (t, 2H), 4.5 (t, 2H), 6.65 (d, 1H), 6.9 (d, 1H), 7.0 (s, 1H); 20 LRMS: $\text{M}+\text{NH}_4$, 208. (ES^+).

PREPARATION 141

4-(2,3-Dihydro-1-benzofuran-5-yl)-2-butanamine

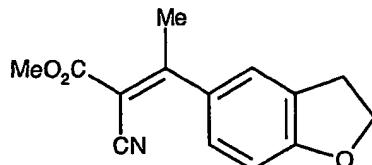


25 To a stirred solution of the product from Preparation 140 (500mg, 2.6mmol) in methanol (25ml) was added ammonium acetate (4.05g, 52.6mmol) and sodium cyanoborohydride (661mg, 10.5mmol) and the whole was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and then partitioned between EtOAc (20ml) and water (20ml). The organics were extracted and washed with water (2x20ml), dried 30 (MgSO_4) and evaporated to a clear oil. This oil was purified by column chromatography

using 5% MeOH in DCM as eluant to give the title product (187mg, 37%); ^1H NMR (400MHz, CDCl_3) δ : 1.3 (d, 3H), 1.8 (m, 2H), 2.6 (m, 2H), 3.1 (t, 2H), 3.2 (m, 1H), 4.45 (t, 2H), 6.6 (d, 1H), 6.9 (d, 1H), 7.05 (s, 1H); LRMS: $\text{M}+\text{H}$, 192. (ES $^+$).

5 PREPARATION 142

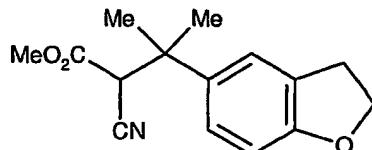
Methyl-(2E)-2-cyano-3-(2,3-dihydro-1-benzofuran-5-yl)-2-butenoate



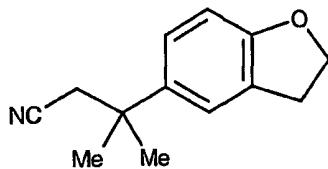
To a stirred solution of 5-acetyl-2,3-dihydrobenzo[b]furan (Aldrich) (1g, 6.17mmol) in toluene (60ml) was added methyl cyanoacetate (0.60ml, 6.78mmol), benzylamine (0.07ml, 0.61mmol) and acetic acid (0.3ml, 5.3mmol) and the whole refluxed in a Dean-Stark apparatus for 16h. The reaction mixture was cooled, washed with 2N HCl (30ml), NaHCO_3 (30ml), brine (30ml), dried (MgSO_4) and evaporated to a yellow residue. This residue was purified by column chromatography using 15-20% EtOAc in pentane as eluant to provide the title product (902mg, 60%); ^1H NMR (400MHz, CDCl_3) δ : 2.65 (s, 3H), 3.25 (t, 2H), 3.9 (s, 3H), 4.6 (t, 2H), 6.8 (d, 1H), 7.25 (d, 1H), 7.8 (s, 1H); LRMS: $\text{M}+\text{NH}_4^+$, 261. (ES $^+$).

PREPARATION 143

Methyl-2-cyano-3-(2,3-dihydro-1-benzofuran-5-yl)-3-methyl-butanoate

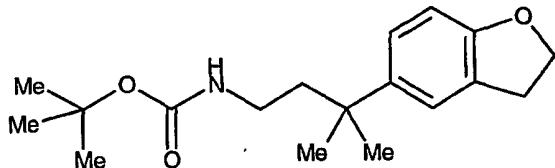


20 Copper (I) iodide (109mg, 0.57mmol) was added to a stirred mixture of MeLi (1.4M in ether, 0.76ml, 1.07mmol) in ether (2ml) at -25°C under nitrogen. After stirring for 10min, a solution of the product from Preparation 142 (100mg, 0.41mmol) in ether (2ml) was added dropwise and the whole then stirred at -25°C for 2h, and the for a further 2h while warming to 0°C. Brine (10ml) was added, and the organics were extracted with EtOAc (10ml), dried (MgSO_4), filtered and evaporated. The residue was then purified by column chromatography using 20% EtOAc in pentane to provide the title product (92mg, 86%); ^1H NMR (400MHz, CDCl_3) δ : 1.55 (d, 6H), 3.2 (m, 2H), 3.59 (s, 3H), 3.62 (s, 1H), 4.5 (t, 2H), 6.7 (d, 1H), 7.1 (d, 1H), 7.2 (s, 1H); LRMS: $\text{M}+\text{NH}_4^+$, 277. (ES $^+$).

PREPARATION 1443-(2,3-Dihydro-1-benzofuran-5-yl)-3-methylbutanenitrile

To a stirred solution of the product from Preparation 143 (400mg, 1.54mmol) in ethanol (1.5ml) and dioxan (1.5ml) was added solid KOH (87mg, 1.54mmol) and the whole stirred at reflux for 6h. The reaction mixture was concentrated *in vacuo* and dissolved in water (15ml). The aqueous layer was washed with toluene (15ml) and then acidified to pH1 with 2N HCl from which the product was extracted with EtOAc (2x20ml). The organic layers were combined, washed with brine (20ml), dried (MgSO_4), filtered and concentrated *in vacuo* to afford an orange oil, which was used with no further purification; ^1H NMR (400MHz, CDCl_3) δ : 1.6 (d, 6H), 3.15 (t, 2H), 3.7 (s, 1H), 4.5 (t, 2H), 6.7 (d, 1H), 7.1 (d, 1H), 7.22 (s, 1H); LRMS: $\text{M}+\text{NH}_4^+$, 263. (ES $^+$). This oil was taken up in DMA (2ml) and heated at 150°C for 2h and then allowed to cool to room temperature and stirred overnight. The reaction mixture was concentrated *in vacuo* and then dissolved in EtOAc (10 ml). The organics were washed with brine (10ml), dried over MgSO_4 , filtered and concentrated *in vacuo* to afford an orange oil. This was purified by column chromatography using 15% EtOAc in pentane as eluant to give the title product (100mg, 32%); ^1H NMR (400MHz, CDCl_3) δ : 1.45 (s, 6H), 2.55 (s, 2H), 3.2 (t, 2H), 4.5 (t, 2H), 6.7 (d, 1H), 7.1 (d, 1H), 7.2 (s, 1H); LRMS: $\text{M}+\text{NH}_4^+$, 219. (ES $^+$).

20

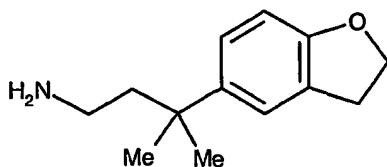
PREPARATION 145tert-Butyl-3-(2,3-dihydro-1-benzofuran-5-yl)-3-methylbutylcarbamate

The product from Preparation 144 (250mg, 1.24mmol) was taken up in methanol (12ml) at 0°C under nitrogen and stirred with di-*tert*-butyl dicarbonate (542mg, 2.48mmol), NiCl_2 (161mg, 1.24mmol) and then NaBH_4 (329mg, 8.69mmol) were added portionwise. The black solution was allowed to warm to room temperature overnight and then was concentrated *in vacuo*. The residue was partitioned between EtOAc (20ml) and NaHCO_3 solution (20ml), the mixture filtered to remove all solids, and the filtrate extracted with EtOAc (2x20ml). The combined organics were dried over MgSO_4 , filtered and evaporated to give the title product (366mg, 96%) which was used with no further

purification; ^1H NMR (400MHz, CDCl_3) δ : 1.25 (s, 6H), 1.35 (s, 9H), 1.7 (t, 2H), 2.9 (brs., 2H), 3.1 (t, 2H), 4.2 (brs., 1H), 4.5 (t, 2H), 6.65 (d, 1H), 7.0 (d, 1H), 7.1 (s, 1H); LRMS: M-BOC, 206. (ES $^+$).

5 **PREPARATION 146**

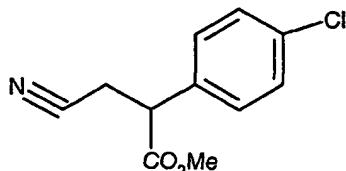
3-(2,3-Dihydro-1-benzofuran-5-yl)-3-methylbutylamine



The product from Preparation 145 (366mg, 1.20mmol) was taken up in DCM (15ml) at 10 0°C and stirred as hydrogen chloride gas was bubbled through the solution for 15min. The flow of HCl was stopped, and the reaction mixture was allowed to warm to room temperature and stirred for 2h. The solution was flooded with ether (20ml), which caused a white precipitate to form. This solid was filtered off, washed with ether and dried under vacuum to give the title product (177mg, 61%); ^1H NMR (400MHz, MeOD) δ : 15 1.3 (s, 6H), 1.9 (m, 2H), 2.6 (m, 2H), 3.1 (m, 2H), 4.5 (m, 2H), 6.6 (s, 1H), 7.01 (s, 1H), 7.2 (s, 1H); LRMS: M+H, 207. (ES $^+$).

PREPARATION 147

Methyl-2-(4-chlorophenyl)-3-cyanopropanoate

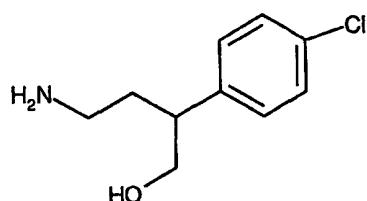


20 To a stirred solution of diisopropylamine (8.65ml, 61.8mmol) in dry THF (100 ml) at -20 $^\circ\text{C}$ under nitrogen was added a 2.5M solution of $^n\text{BuLi}$ in hexanes (23.7ml, 59.2mmol) dropwise. The solution was allowed to warm to 0 $^\circ\text{C}$ over 20min, and then cooled to -70 $^\circ\text{C}$. A solution of methyl-2-(4-chlorophenyl)acetate (9.5g, 51.5mmol) in THF (5 ml) 25 was added dropwise over 5min, and the whole then stirred for 30min. Iodoacetonitrile (5.03ml, 69.5mmol) was then added slowly, and the combined solution allowed to warm to room temperature over 72h. Saturated aq. NaHCO_3 solution (20 ml) was added, the mixture was concentrated to about 50ml under vacuum, and then treated with 1N HCl (100ml). The mixture was extracted with EtOAc (120 ml) which was dried (MgSO_4) and 30 evaporated to give a dark brown oil, which was purified by column chromatography using

2:1 DCM:pentane as eluant to give the title product (8.6g, 75%); ^1H NMR (400MHz, CDCl_3) δ : 2.80 (dd, 1H), 3.00 (d, 1H), 3.73 (s, 3H), 3.92 (dd, 1H), 7.22 (d, 2H), 7.37 (d, 2H).

5 PREPARATION 148

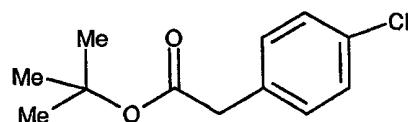
4-Amino-2-(4-chlorophenyl)butanol



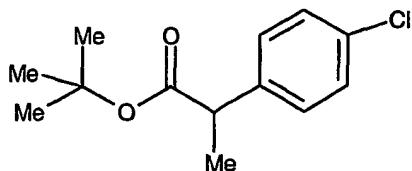
The product from Preparation 147 (235mg, 1.05mmol) was taken up in 1ml THF and added dropwise to a stirred solution of LiAlH_4 (2.1ml, 1M solution in THF, 2.1mmol) in 10 THF at 0°C under nitrogen. The mixture was then stirred at room temperature for 2h, and cooled to 0°C. Water (0.08 ml) was added, followed by 3N aqueous solution of NaOH (0.08 ml) and the whole then diluted with THF (2ml) and water (0.24ml). The suspension was stirred for 5min, and then filtered and the filtrate evaporated to a yellow gum. This was taken up in EtOAc (5 ml) and extracted with 0.5N HCl solution (0.3 ml), 15 which was then basified with Na_2CO_3 solution to pH10 and extracted with EtOAc (5x3ml). The combined organics were dried (MgSO_4) and evaporated to give the title product (60mg, 29%); ^1H NMR (400MHz, CDCl_3) δ : 1.62-1.95 (m, 2H), 2.58-3.00 (m, 3H), 3.58-3.80 (m, 2H), 7.02-7.39 (m, 4H).

20 PREPARATION 149

tert-Butyl-(4-chlorophenyl)acetate



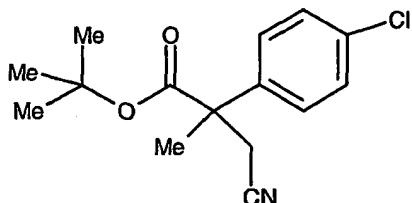
To a suspension of *N,N*-dimethyl-formamide-di-*tert*-butyl acetal (25ml, 104.4mmol) in dry 25 toluene (90 ml) was added *p*-chlorophenyl acetic acid (5.94g, 34.8mmol) and the whole heated at 80°C for 1h. The mixture was diluted with EtOAc (50 ml) and washed with water (50 ml), 3% aqueous NaHCO_3 solution (50 ml) and brine (20ml) and then dried over MgSO_4 and evaporated to give an oil. This oil was purified using 35%, then 50% DCM in pentane to give the title product (2.4g, 30%); ^1H NMR (400MHz, CDCl_3) δ : 1.42 30 (s, 9H), 3.44 (s, 2H), 7.20 (d, 2H), 7.28 (d, 2H).

PREPARATION 150tert-Butyl-2-(4-chlorophenyl)propanoate

5

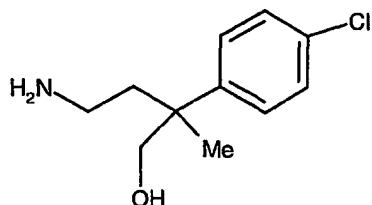
The product from Preparation 149 was alkylated according to an identical procedure to that described in Preparation 147, using methyl iodide as the alkylating agent. The title product was obtained in 95% yield after purification by column chromatography using 25% DCM in pentane as eluant; ^1H NMR (400MHz, CDCl_3) δ : 1.39 (s, 9H), 1.41 (d, 3H),

10 3.59 (q, 1H), 7.20 (d, 2H), 7.25 (d, 2H).

PREPARATION 151

The product from Preparation 150 was alkylated according to an identical procedure to that described in Preparation 137. The title product was obtained in 82% yield after purification by column chromatography, using 35%, then 70% DCM in pentane as eluant; ^1H NMR (400MHz, CDCl_3) δ : 1.40 (s, 9H), 1.74 (s, 3H), 2.80 (d, 1H), 2.95 (d, 1H), 7.24 (d, 2H), 7.35 (d, 2H).

20 PREPARATION 152

4-Amino-2-(4-chlorophenyl)-2-methylbutanol

The product from Preparation 151 was reduced with LiAlH_4 according to the procedure of Preparation 148 to provide the title product (35%). The product of this reduction was sufficiently pure that it warranted no further purification; ^1H NMR (400MHz, CDCl_3) δ : 1.22

(s, 3H), 1.71 (ddd, 1H), 2.01 (ddd, 1H), 2.60 (ddd, 1H), 2.83 (ddd, 1H), 3.60 (d, 1H), 3.82 (d, 1H), 7.27 (d, 2H), 7.38 (d, 2H).

Biological Assays

5 IC₅₀ values of the compounds of the invention against NEP and ACE were determined using methods described in published patent application EP1097719-A1, paragraphs [0368] to [0376]. The IC₅₀ values presented below were determined using NEP from canine kidney. In addition, the IC₅₀ value of some compounds of the invention were determined using NEP from human kidney; these values were similar to the values
10 determined using canine NEP.

The compounds of the invention are potent inhibitors of NEP and are selective against ACE.

15 The title compounds of Examples herein showed an IC₅₀ against NEP of less than 400 nM.

The title compounds of Examples 1-25, 27-37, 39-41, 43-48, 50-53 and 55- 67 showed an IC₅₀ against NEP of less than or equal to 150 nM and a selectivity over ACE of
20 greater than 300 fold.

In particular, the title compound of Example 3 showed an IC₅₀ against NEP of 22 nM; the title compound of Example 4 showed an IC₅₀ against NEP of 4 nM; the title compound of Example 21 showed an IC₅₀ against NEP of 3 nM; the title compound of
25 Example 33 showed an IC₅₀ against NEP of 47 nM; the title compound of Example 43 showed an IC₅₀ against NEP of 29 nM; and the title compound of Example 51 showed an IC₅₀ against NEP of 9 nM. The title compounds of Examples 3, 4, 21, 33, 43 and 51 were all greater than 300 fold selective against ACE.

30 Animal Model of Female Sexual Arousal Response

The title compound from Example 22 (herein after referred to as "the selected compound") was administered according to the protocol described in EP1097719-A1, paragraphs [0495] to [0499]. The selected compound was made up in 5% saline. The selected compound and vehicle controls were infused using a Harvard 22 pump, infusing
35 at 500 μ l/min via a 3-way tap into the femoral vein. After the infusion, the catheter was

flushed with heparinised saline (Hepsaline) so that none of the selected compound was left in the catheter.

The selected compound, tested at clinically relevant doses, significantly enhanced pelvic nerve stimulated increases in genital blood flow (See Figure 1). The selected compound enhanced the peak increase in vaginal blood flow by up to 56% (n=3) and clitoral blood flow by 50% (n=3) compared to time matched control increases.

Figure 1 shows the effect of administering the selected compound on the genital blood flow in a rabbit. The selected compound enhanced pelvic nerve stimulated (PNS) increases in genital blood flow in the anaesthetised rabbit model of sexual arousal. Repetitive PNS at 15 minute intervals induced reproducible increases in genital blood flow (Hatched Bars). Administration of the elected compound (Grey bar) enhanced the peak increase in clitoral and vaginal blood flow induced by submaximal stimulation frequencies (eg 4Hz) compared to increases observed during time matched control stimulations or vehicle controls (Hatched bar). The following simultaneous enhancements were observed following an approximate 0.5mg/kg iv bolus – a 50% increase in clitoral and a 56% increase in vaginal blood flow (n=3). Data expressed as mean \pm sem; all changes were monitored using laser Doppler technologies.

There were no major effects of NEP inhibition or on basal/un-stimulated genital blood flow.

Female New Zealand rabbits (~2.5kg) were pre-medicated with a combination of Medetomidine (Domitor®) 0.5ml/kg *i.m.*, and Ketamine (Vetalar®) 0.25ml/kg *i.m.* whilst maintaining oxygen intake via a face mask. The rabbits were tracheotomised using a Portex™ uncuffed endotracheal tube 3 ID., connected to ventilator and maintained at a ventilation rate of 30-40 breaths per minute, with an approximate tidal volume of 18-20 ml, and a maximum airway pressure of 10 cm H₂O. Anaesthesia was then switched to Isoflurane and ventilation continued with O₂ at 2l/min. The right marginal ear vein was cannulated using a 23G or 24G catheter, and Lactated Ringer solution perfused at 0.5ml/min. The rabbit was maintained at 3% Isoflurane during invasive surgery, dropping to 2% for maintenance anaesthesia.

The left groin area of the rabbit was shaved and a vertical incision was made approximately 5cm in length along the thigh. The femoral vein and artery were exposed,

isolated and then cannulated with a PVC catheter (17G) for the infusion of drugs and compounds. Cannulation was repeated for the femoral artery, inserting the catheter to a depth of 10cm to ensure that the catheter reached the abdominal aorta. This arterial catheter was linked to a Gould system to record blood pressure. Samples for blood gas analysis were also taken via the arterial catheter. Systolic and diastolic pressures were measured, and the mean arterial pressure calculated using the formula (diastolic x2 + systolic) ÷3. Heart rate was measured via the pulse oxymeter and *Po-ne-mah* data acquisition software system (Ponemah Physiology Platform, Gould Instrument Systems Inc).

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A ventral midline incision was made into the abdominal cavity. The incision was about 5cm in length just above the pubis. The fat and muscle was *bluntly* dissected away to reveal the hypogastric nerve which runs down the body cavity. It was essential to keep close to the side curve of the pubis wall in order to avoid damaging the femoral vein and artery which lie above the pubis. The sciatic and pelvic nerves lie deeper and were located after further dissection on the dorsal side of the rabbit. Once the sciatic nerve is identified, the pelvic nerve was easily located. The term *pelvic nerve* is loosely applied; anatomy books on the subject fail to identify the nerves in sufficient detail. However, stimulation of the nerve causes an increase in vaginal and clitoral blood flow, and innervation of the pelvic region. The pelvic nerve was freed away from surrounding tissue and a *Harvard* bipolar stimulating electrode was placed around the nerve. The nerve was slightly lifted to give some tension, then the electrode was secured in position. Approximately 1ml of light paraffin oil was placed around the nerve and electrode. This acts as a protective lubricant to the nerve and prevents blood contamination of the electrode. The electrode was connected to a *Grass S88 Stimulator*. The pelvic nerve was stimulated using the following parameters:- 0.5-5V, pulse width 0.5ms, duration of stimulus 10 seconds and a frequency range of 2 to 16Hz. Reproducible responses were obtained when the nerve was stimulated every 15-20 minutes. A frequency response curve was determined at the start of each experiment in order to determine the optimum frequency to use as a sub-maximal response, normally 4Hz. The compound(s) to be tested were infused, via the femoral vein, using a *Harvard 22* infusion pump allowing a continuous 15 minute stimulation cycle.

35 A ventral midline incision was made, at the caudal end of the pubis, to expose the pubic area. Connective tissue was removed to expose the tunica of the clitoris, ensuring that the wall was free from small blood vessels. The external vaginal wall was also exposed

by removing any connective tissue. One laser Doppler flow probe was inserted 3cm into the vagina, so that half the probe shaft was still visible. A second probe was positioned so that it lay just above the external clitoral wall. The position of these probes was then adjusted until a signal was obtained. A second probe was placed just above the surface 5 of a blood vessel on the external vaginal wall. Both probes were clamped in position. Vaginal and clitoral blood flow was recorded either as numbers directly from the Flowmeter using *Po-ne-mah* data acquisition software (Ponemah Physiology Platform, Gould Instrument Systems Inc), or indirectly from Gould chart recorder trace. Calibration was set at the beginning of the experiment (0-125ml/min/100g tissue).

10

Animal model of Male Erectile Response

Anaesthetised Rabbit Methodology

The title compound from Example 22 ("the selected compound") alone and in 15 combination with the selective and potent PDE5 inhibitor 3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulfonyl)-2-n-propoxyphenyl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one were administered in accordance with the following protocol. The selected compound was made up in saline + 5% 1M NaOH. The selected compound and vehicle controls were infused using a Harvard 22 pump, infusing at 500 μ l/min via a 20 3-way tap into the femoral vein. After the infusion, the catheter was flushed with heparinised saline (Hepsaline) so that none of the selected compound was left in the catheter. The PDE5 inhibitor was made up in saline + 5% 1M HCl, the compounds and vehicle controls were infused at a rate of 0.1ml/second and left for 15 minutes prior to pelvic nerve stimulation.

25

Two experiments were performed: the effect on Intracavernosal pressure (ICP) of administering a) the selected compound alone, and b) in combination with a PDE5 inhibitor. The effect on ICP is shown in Figure 2. Data is expressed as the mean percentage (%) increase \pm s.e.mean. * P<0.01, Students t-test unpaired compared with 30 control increases.

Administration of the selected compound alone resulted in a 37 \pm 7% potentiation of submaximally stimulated intracavernosal pressure was observed (see Figure 2, light grey column; n=4).

35

Administration of a combination of the selected compound with a selective PDE5 inhibitor (1mg/kg iv bolus) resulted in a 70±4% potentiation of submaximally stimulated intracavernosal pressure (see Figure 2, dark grey column; n=3).

5 There were no major effects of NEP inhibition or concomitant NEP/PDE5 inhibition on basal/un-stimulated intracavernosal pressure.

Male New Zealand rabbits (~2.5kg) were pre-medicated with a combination of Medetomidine (Domitor®) 0.5ml/kg *i.m.*, and Ketamine (Vetalar®) 0.25ml/kg *i.m.* whilst 10 maintaining oxygen intake via a face mask. The rabbits were tracheotomised using a Portex™ uncuffed endotracheal tube 3 ID., connected to ventilator and maintained at a ventilation rate of 30-40 breaths per minute, with an approximate tidal volume of 18-20 ml, and a maximum airway pressure of 10 cm H₂O. Anaesthesia was then switched to Isoflurane and ventilation continued with O₂ at 2l/min. The right marginal ear vein was 15 cannulated using a 23G or 24G catheter, and Lactated Ringer solution perfused at 0.5ml/min. The rabbit was maintained at 3% Isoflurane during invasive surgery, dropping to 2% for maintenance anaesthesia. The left jugular vein was exposed, isolated and then cannulated with a PVC catheter (17G) for the infusion of the selected compound or combination thereof.

20 The left groin area of the rabbit was shaved and a vertical incision was made approximately 5cm in length along the thigh. The femoral vein and artery were exposed, isolated and then cannulated with a PVC catheter (17G) for infusion of the selected compound or combination thereof. Cannulation was repeated for the femoral artery, 25 inserting the catheter to a depth of 10cm to ensure that the catheter reached the abdominal aorta. This arterial catheter was linked to a Gould system to record blood pressure. Samples for blood gas analysis were also taken via the arterial catheter. Systolic and diastolic pressures were measured, and the mean arterial pressure calculated using the formula (diastolic x2 + systolic) ÷3. Heart rate was measured via the 30 pulse oximeter and *Po-ne-mah* data acquisition software system (Ponemah Physiology Platform, Gould Instrument Systems Inc).

A ventral midline incision was made into the abdominal cavity. The incision was about 5cm in length just above the pubis. The fat and muscle was *bluntly* dissected away to 35 reveal the hypogastric nerve which runs down the body cavity. It was essential to keep close to the side curve of the pubis wall in order to avoid damaging the femoral vein and

artery which lie above the pubis. The sciatic and pelvic nerves lie deeper and were located after further dissection on the dorsal side of the rabbit. Once the sciatic nerve is identified, the pelvic nerve was easily located. The term *pelvic nerve* is loosely applied; anatomy books on the subject fail to identify the nerves in sufficient detail. However,

5 stimulation of the nerve causes an increase in intracavernosal pressure and cavernosal blood flow, and innervation of the pelvic region. The pelvic nerve was freed away from surrounding tissue and a *Harvard* bipolar stimulating electrode was placed around the nerve. The nerve was slightly lifted to give some tension, then the electrode was secured in position. Approximately 1ml of light paraffin oil was placed around the nerve

10 and electrode. This acts as a protective lubricant to the nerve and prevents blood contamination of the electrode. The electrode was connected to a *Grass S88* Stimulator. The pelvic nerve was stimulated using the following parameters:- 0.5-5V, pulse width 0.5ms, duration of stimulus 20 seconds with a frequency of 2-16Hz. Reproducible responses were obtained when the nerve was stimulated every 15-20 minutes. Several

15 stimulations using the above parameters were performed to establish a mean control response. The selected compound or combination thereof was infused, via the jugular vein, using a *Harvard 22* infusion pump allowing a continuous 15 minute stimulation cycle. The skin and connective tissue around the penis was removed to expose the penis. A catheter set (*Insyte-W*, Becton-Dickinson 20 Gauge 1.1 x 48mm) was inserted

20 through the tunica albica into the left *corpus cavernosal* space and the needle removed, leaving a flexible catheter. This catheter was linked via a pressure transducer (Ohmeda 5299-04) to a Gould system to record intracavernosal pressure. Once an intracavernosal pressure was established, the catheter was sealed in place using *Vetbond* (tissue adhesive, 3M). Heart rate was measured via the pulse oxymeter and

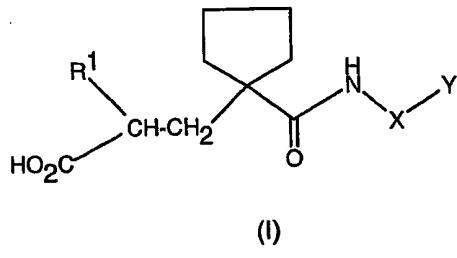
25 *Po-ne-mah* data acquisition software system (Ponemah Physiology Platform, Gould Instrument Systems Inc).

Intracavernosal blood flow was recorded either as numbers directly from the Flowmeter using *Po-ne-mah* data acquisition software (Ponemah Physiology Platform, Gould

30 Instrument Systems Inc), or indirectly from Gould chart recorder trace. Calibration was set at the beginning of the experiment (0-125ml/min/100g tissue).

Claims

1 A compound of formula (I), a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof;



5 wherein

R¹ is C₁₋₆alkyl which may be substituted by one or more substituents, which may be the same or different, selected from the list: halo, hydroxy, C₁₋₆alkoxy, hydroxyC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkoxy, carbocyclyl, carbocyclyloxy, C₁₋₄alkoxycarbocyclyloxy, heterocyclyl, heterocyclyloxy, -NR²R³, -NR⁴COR⁵, -NR⁴SO₂R⁵, -CONR²R³, -S(O)_pR⁶, -COR⁷ and -CO₂(C₁₋₄alkyl); or R¹ is carbocyclyl or heterocyclyl, each of which may be substituted by one or more substituents from said list, which substituents may be the same or different, which list further includes C₁₋₆alkyl; or R¹ is hydrogen, C₁₋₆alkoxy, -NR²R³ or -NR⁴SO₂R⁵;

10 wherein

R² and R³, which may be the same or different, are carbocyclyl or heterocyclyl (each of which may be substituted by C₁₋₄alkyl, hydroxy or C₁₋₄alkoxy); or are hydrogen or C₁₋₄alkyl; or R² and R³ together with the nitrogen to which they are attached form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C₁₋₄alkyl)piperazinyl group;

15 R⁴ is hydrogen or C₁₋₄alkyl;

R⁵ is C₁₋₄alkyl, CF₃, carbocyclyl, C₁₋₄alkylcarbocyclyl, C₁₋₄alkoxycarbocyclyl, heterocyclyl, C₁₋₄alkoxy or -NR²R³;

20 R⁶ is C₁₋₄alkyl, carbocyclyl, heterocyclyl or NR²R³; and

R⁷ is C₁₋₄alkyl, carbocyclyl or heterocyclyl;

25 p is 0, 1, 2 or 3;

X is the linkage $-(CH_2)_n-$ or $-(CH_2)_q-O-$ (wherein Y is attached to the oxygen);
wherein one or more hydrogen atoms in linkage X may be replaced
independently by C₁₋₄alkoxy; hydroxy; hydroxyC₁₋₃alkyl; C₃₋₇cycloalkyl;
carbocyclyl; heterocyclyl; or by C₁₋₄alkyl optionally substituted by one or
5 more fluoro or phenyl groups; n is 3, 4, 5, 6 or 7; and q is 2, 3, 4, 5 or 6;
and

Y is phenyl or pyridyl, each of which may be substituted by one or more groups
R⁸ which may be the same or different, wherein R⁸ is hydroxy; mercapto;
halogen; cyano; acyl; amino; mono(C₁₋₄alkyl)amino; di(C₁₋₄alkyl)amino;
10 carbocyclyl or heterocyclyl (either of which is optionally substituted by
C₁₋₆alkyl, haloC₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkoxy, C₁₋₆alkylthio or
halogen); C₁₋₆alkoxy; phenoxy; C₁₋₆alkylthio; phenylthio; or alkyl
optionally substituted by C₁₋₆alkoxy, haloC₁₋₆alkoxy, C₁₋₆alkylthio,
halogen or phenyl; or

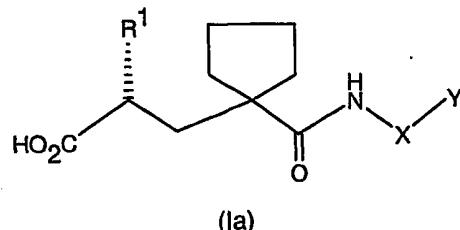
15 two R⁸ groups on adjacent carbon atoms together with the interconnecting
carbon atoms may form a fused 5- or 6-membered carbocyclic or
heterocyclic ring, optionally substituted by C₁₋₆alkyl, haloC₁₋₆alkyl,
C₁₋₆alkoxy, haloC₁₋₆alkoxy, C₁₋₆alkylthio or halogen.

20 2 A compound according to claim 1, a pharmaceutically acceptable salt, solvate,
polymorph or prodrug thereof, wherein R¹ is hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy,
C₁₋₆alkoxyC₁₋₃alkyl, C₁₋₆alkoxyC₁₋₆alkoxyC₁₋₃alkyl or C₁₋₆alkyl substituted by
phenyl.

25 3 A compound according to claim 2, a pharmaceutically acceptable salt, solvate,
polymorph or prodrug thereof, wherein R¹ is hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy,
C₁₋₆alkoxyC₁₋₃alkyl or C₁₋₆alkoxyC₁₋₆alkoxyC₁₋₃alkyl.

30 4 A compound according to claim 3, a pharmaceutically acceptable salt, solvate,
polymorph or prodrug thereof, wherein R¹ is C₁₋₄alkyl or C₁₋₆alkoxyC₁₋₃alkyl.

5 5 A compound according to any preceding claim, a pharmaceutically acceptable
salt, solvate, polymorph or prodrug thereof, of formula Ia:



6 A compound according to any preceding claim, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof wherein X is $-(CH_2)_n-$ and wherein
5 one or more hydrogen atoms in linkage X may be replaced by one or more of the groups defined claim 1.

7 A compound according to any preceding claim, pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein when present n is 3 or 4.

10 8 A compound according to any preceding claim, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein R^8 is C_1 - 6 alkyl, C_1 - 6 alkoxy, hydroxy, mercapto, halo, cyano, carbocyclyl or heterocyclyl; or two R^8 groups on adjacent carbon atoms together with the interconnecting carbon atoms may form a fused 5- or 6-membered carbocyclic or heterocyclic ring, optionally substituted by C_1 - 6 alkyl, halo C_1 - 6 alkyl, C_1 - 6 alkoxy, halo C_1 - 6 alkoxy, C_1 - 6 alkylthio or halogen.

15 9 A compound according to any preceding claim, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein when R^8 is carbocyclyl, R^8 is cyclopentyl, cyclopropyl, cyclohexyl or phenyl.

20 10 A compound according to any one of claims 1 to 8, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein when R^8 is heterocyclyl, R^8 is pyridyl, oxadiazolyl, pyrazolyl or triazolyl.

25 11 A compound according to any one of claim 1 to 8, a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof, wherein when Y is phenyl and two R^8 groups on adjacent carbon atoms together with the interconnecting carbon atoms form a fused 5- or 6-membered carbocyclic or heterocyclic ring, the fused ring systems are naphthyl, quinolinyl, isoquinolinyl, indolyl, indazolyl, benzimidazolyl,

30

benzisoxazolyl, dihydrobenzofuranyl, benzoxazolyl, indanyl, benzisothiazolyl and benzothiazolyl.

12 A compound according to claim 1, a pharmaceutically acceptable salt, solvate,
5 polymorph or prodrug thereof, wherein the compound is:

(2*R*)-2-{[1-({[3-(4-methoxyphenyl)propyl]amino}carbonyl)cyclopentyl]methyl}-
pentanoic acid (Example 16);

10 3-{[1-({[3-(4-methoxyphenyl)propyl]amino}carbonyl)cyclopentyl]propanoic acid
(Example 18);

3-{[1-({[3-(2,3-dihydro-1-benzofuran-5-yl)propyl]amino}carbonyl)cyclopentyl]-
propanoic acid (Example 21);

2-{[1-({[3-(4-chlorophenyl)propyl]amino}carbonyl)cyclopentyl]methyl}-4-
methoxybutanoic acid (Example 15);

15 2-{[1-({[3-(4-fluorophenyl)propyl]amino}carbonyl)cyclopentyl]methyl}-4-
methoxybutanoic acid (Example 4);

4-methoxy-2-{[1-({[3-(4-methoxyphenyl)propyl]amino}carbonyl)cyclopentyl]-
methyl]butanoic acid (Example 1);

20 2-{[1-({[3-(2,3-dihydro-1-benzofuran-5-yl)propyl]amino}carbonyl)cyclopentyl]-
methyl}-4-methoxybutanoic acid (Example 11);

(2*S*)-2-{[1-({[3-(4-chlorophenyl)propyl]amino}carbonyl)cyclopentyl]methyl}-4-
methoxybutanoic acid (Example 22); and

(2*S*)-2-{[1-({[3-(2,3-dihydro-1-benzofuran-5-yl)propyl]amino}carbonyl)cyclopentyl]-
methyl}-4-methoxybutanoic acid (Example 25).

25 13 (2*S*)-2-{[1-({[3-(4-Chlorophenyl)propyl]amino}carbonyl)cyclopentyl]methyl}-4-
methoxybutanoic acid (Example 22).

14 The use of a compound defined in any preceding claim, a pharmaceutically
30 acceptable salt, solvate, polymorph or prodrug thereof, in the manufacture of a
medicament for treating or preventing a condition for which a beneficial response
is obtained by the inhibition of neutral endopeptidase.

15 The use according to claim 14 wherein the condition is Female Sexual
35 Dysfunction or Male Erectile Dysfunction.

16 The use according to claim 15 wherein the condition is Female Sexual Arousal
Disorder.

17 The use according to any one of claims 14 to 16 wherein the compound is
5 administered systemically.

18 The use according to claim 17 wherein the compound is administered orally.

19 The use according to any one of claims 14 to 16 wherein the compounds are
10 administered topically.

20 A compound defined in any one of claims 1 to 13, a pharmaceutically acceptable
salt, solvate, polymorph or prodrug thereof, for use as a medicament.

15 21 A method of treating or preventing a condition for which a beneficial response is
obtained by the inhibition of neutral endopeptidase in a mammal comprising
treating said mammal with a therapeutically effective amount of a compound
defined in any one of claims 1 to 13, a pharmaceutically acceptable salt, solvate,
polymorph or prodrug thereof.

20 22 The method of claim 21 wherein the condition is defined in claim 15 or 16.

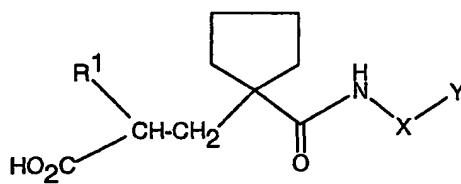
23 A pharmaceutical composition including a compound defined in any one of claims
1 to 13, a pharmaceutically acceptable salt, solvate, polymorph or prodrug
25 thereof together with a pharmaceutically acceptable excipient, diluent or carrier.

24 A combination of a compound defined in any one of claims 1 to 13 and one or
more active ingredients selected from the list:
a) a PDE5 inhibitor, more preferably 5-[2-ethoxy-5-(4-methyl-1-
30 piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-
pyrazolo[4,3-d]pyrimidin-7-one (sildenafil); (6R,12aR)-2,3,6,7,12,12a-
hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl) -
pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (IC-351); 2-[2-ethoxy-5-(4-
ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-
35 imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil); 5-[2-ethoxy-5-(4-
ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-

dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one and pharmaceutically acceptable salts thereof;

- 5 b) an NPY Y1 inhibitor;
- c) a dopamine agonist such as apomorphine or a selective D₂, D₃ or D₂/D₃agonist such as, pramipexole and ropinirol;
- d) a melanocortin receptor agonist or modulator or melanocortin enhancer, preferably melanotan II, PT-14, PT-141;
- e) an agonist, antagonist or modulator for 5HT2C;
- 10 f) an estrogen receptor modulator, estrogen agonists and/or estrogen antagonists, preferably raloxifene, tibolone or lasoxifene;
- g) an androgen such as androsterone, dehydro-androsterone, testosterone, androstanedione and a synthetic androgen; and
- h) an oestrogen, such as oestradiol, oestrone, oestriol and a synthetic estrogen, such as oestrogen benzoate.

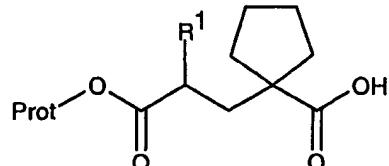
15 25 A process for the preparation of a compound of general formula I



(I)

wherein R¹, X and Y are as defined in any one of claims 1 to 13 or salts thereof
20 comprising the steps of:

- a) reacting a compound of formula II

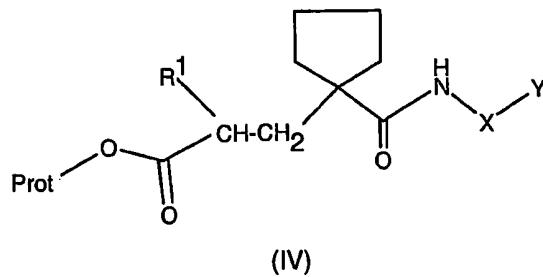


(II)

wherein Prot is a suitable protecting group, with a compound of formula III

25 Y-X-NH₂ (III)

to give a compound of formula IV;

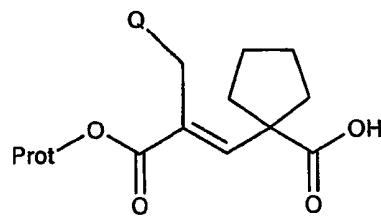
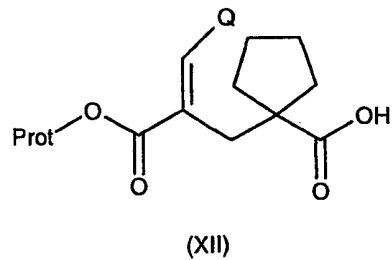
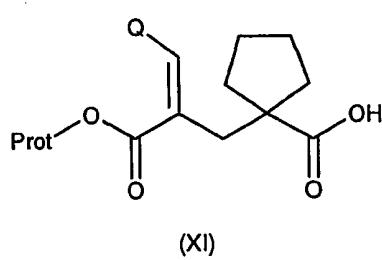


then

5 b) reacting compound of formula IV under suitable deprotecting conditions to give the compound of formula I; then

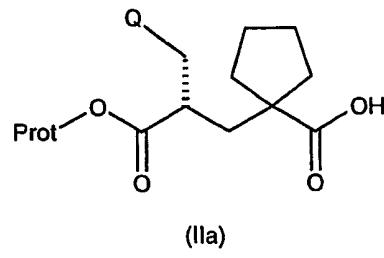
c) optionally forming a salt.

26 A process according to claim 25 further comprising asymmetric hydrogenation of any one of compounds of formula XI, XII or XIII

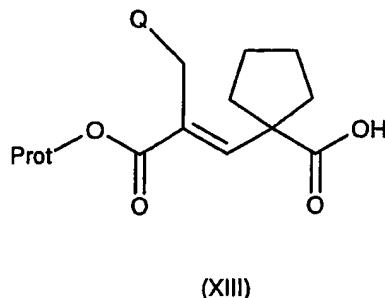
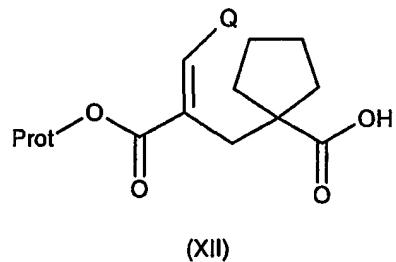
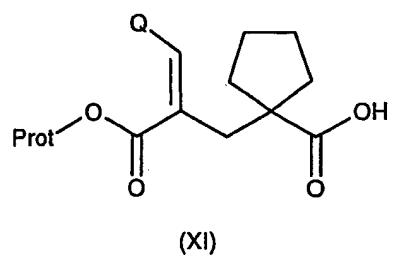


(XIII)

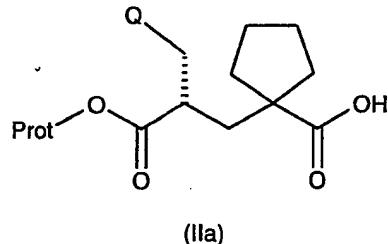
10 where Q is the substituent on the C₁₋₆alkyl group defined for R¹ in claim 1, to give a compound of formula IIa



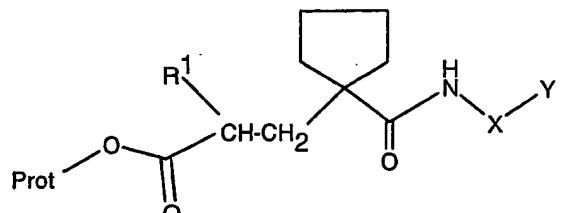
27 A process comprising asymmetric hydrogenation of any one of compounds of formula XI, XII or XIII



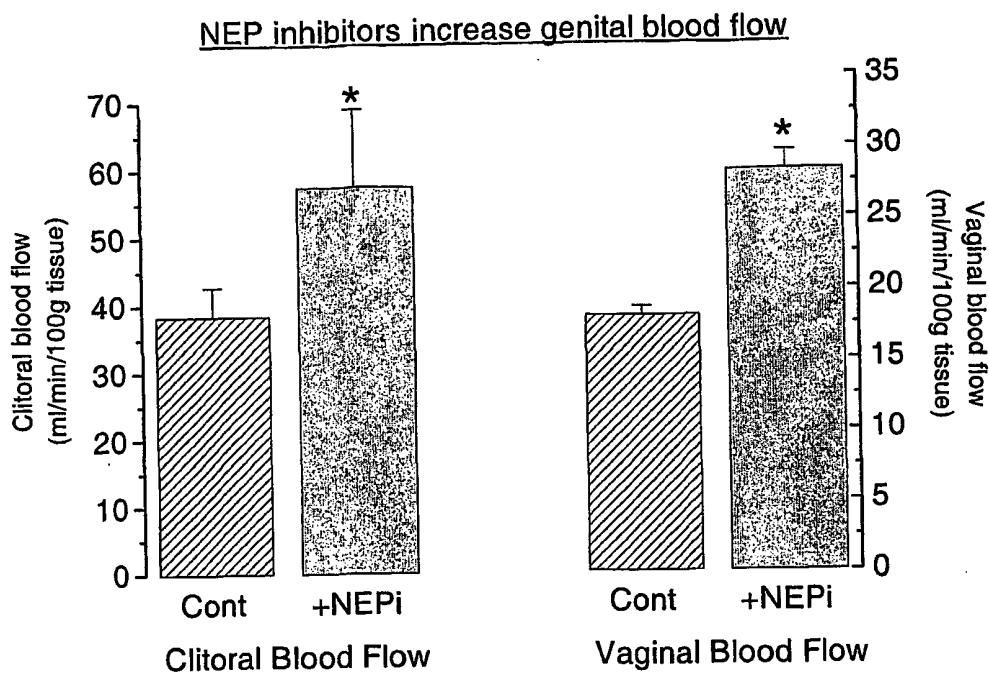
5 where Q is the substituent on the C₁-alkyl group defined for R¹ in claim 1 and
Prot is a suitable protecting group, to give a compound of formula IIa



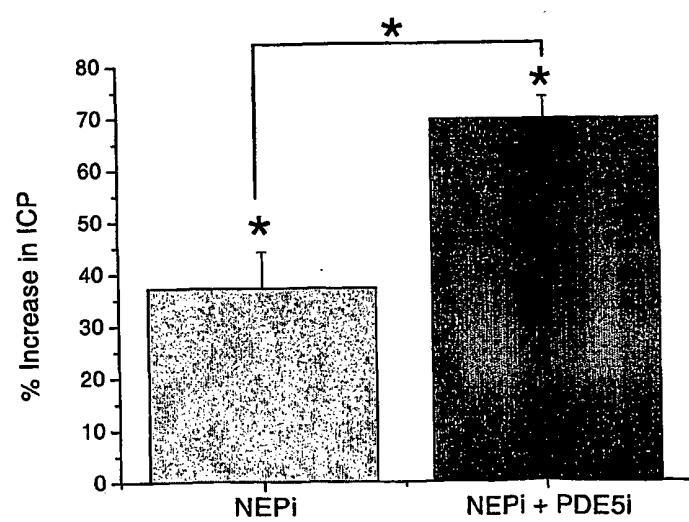
28 A compound of formula IV



wherein R¹, X and Y are as defined in any one of claims 1 to 13 and wherein Prot is a suitable protecting group.

Figure 1Figure 2

5

NEP inhibitors increase Intracavernosal Pressure (ICP)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 02/00807

| | | | | |
|-------------------------------------|------------|------------|------------|------------|
| A. CLASSIFICATION OF SUBJECT MATTER | | | | |
| IPC 7 | C07C235/82 | C07C255/60 | C07D231/56 | C07D311/74 |
| | C07D307/79 | C07D213/40 | C07D215/12 | C07D319/20 |
| | A61K31/195 | A61K31/335 | A61K31/41 | A61K31/435 |

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | WO 91 13054 A (PFIZER) 5 September 1991 (1991-09-05) page 16, line 21 -page 17, line 22; claims; examples --- | 1,14,21, 23,24,28 |
| A | WO 91 10644 A (PFIZER) 25 July 1991 (1991-07-25) page 1, line 11 -page 2, line 7; claims; examples --- | 1,14,21, 23,24,28 |
| A | WO 94 06756 A (SCHERING) 31 March 1994 (1994-03-31) page 2, line 3 -page 3, line 5; claims; examples --- | 1,14,21, 23,24,28 |
| P, A | WO 02 02513 A (PFIZER) 10 January 2002 (2002-01-10) claims; figures; examples --- | 1,14,21, 23,24,28 |

 Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the International search

Date of mailing of the International search report

14 June 2002

24/06/2002

Name and mailing address of the ISA
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Authorized officer

Zervas, B

INTERNATIONAL SEARCH REPORT

I..... tional application No.
PCT/IB 02/00807

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 21 and 22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 1-12, 14-23 (all in part) because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-12, 14-23 (all in part)

The scope of the claims 1 - 12 and 14 to 23 in as far as the expression "prodrug" is concerned, is so unclear (article 6 PCT) that a meaningful International Search is impossible with regard to this expression.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 02/00807

| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
|--|---|------------------|--|--|--|
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